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VOLUME LXV MARCH, 1955 NUMBER 3

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THE
LARYNGOSCOPE.

VOL. LXV MARCH, 1955. No. 3

CLINICAL APPLICATIONS OF RECRUITMENT AND MASKING.*

FREDERICK HARBERT, M.D.,
and
JOSEPH A. SATALOFF, M.D.,
Philadelphia, Pa.

CLINICAL APPLICATION OF RECRUITMENT.

The purpose of this presentation is to invite attention to the diagnostic and prognostic values of recruitment studies, and to advocate their routine use in cases of perceptive deafness. Recruitment of loudness occurs predominantly in pathologic ears, and is an abnormally large growth in the sensation of loudness as compared to the increase in the physical intensity of the signal. Since loudness is a psychological phenomenon, it requires a subjective judgment from the patient. There is, as yet, no truly objective method of measuring recruitment.

The patient whose ear recruits generally presents some of the following symptoms:

1. Distortion is probably present if the patient complains of voices or music sounding tinny, hollow, or fuzzy.

2. Diplacusis is present if a tuning fork has a different pitch in the recruiting than in the nonrecruiting ear. The pitch usually sounds higher in the recruiting ear. The frequency of the fork should be one in which a well marked hearing defect is present.

* Read at the meeting of the Eastern Section, American Laryngological, Rhinological and Otological Society, Inc., Philadelphia, Pa., January 7, 1955.
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3. A lowered threshold of discomfort is implied if loud noises, ordinarily well tolerated by the normal ear, produce discomfort. A loud tuning fork, for example, will cause the patient to wince or sharply withdraw his head. This will not occur in the nonrecruiting ear.

4. The patient with recruitment usually has much sharper, more definite, audiometric end points than found in conductive losses.

5. Variable hearing occurs specifically in labyrinthosis, and is unlike the subjective daily variations found in conductive and functional hearing losses. In labyrinthosis there may be poor hearing for days, weeks, or months followed by improvement. These changes can occur intermittently and are demonstrable on the audiogram.

For clinical purposes the alternate loudness balance test, first described by Fowler, is a practical method to determine recruitment. This test requires at least a 20 db difference in threshold between the two ears in the frequency being tested; that is, if one ear is normal or the pathology is the same in both ears. If the pathology differs in each ear, recruitment of loudness may still be apparent, even though the thresholds are the same as demonstrated by Dr. Harbert (see Fig. 4).

The monaural loudness balance test can also be used in clinical practice, but should be interpreted with full appreciation of the difficulties in comparing the loudness of two tones of different pitches. This difficulty is even apparent in the alternate loudness balance test when diplacusis is present, for patients will often complain of uncertainty in loudness comparison, because the pitch sounds differently in either ear.

Difference limen testing, that is, determining the intensity difference between two sounds which is just perceptible as a change in loudness, gives promise of being a useful technique for determining recruitment, but it is still in the investigative stage. In our hands the Luscher Test, as available on a commercial instrument, has not added to our clinical information.

The manner in which any of these tests is performed is of utmost importance for a valid interpretation. Hood, for ex-

ample, has shown that when a recruiting ear is exposed to a continuous stimulus, such as used in a Bekesy type audiometer, a pathologic adaptation occurs and may cause recruitment to disappear completely. Consequently, it is essential to use only short bursts of tone when performing loudness balance testing.

According to the most widely accepted concepts, a recruiting ear indicates a lesion in the organ of Corti. Recruitment is not present in a lesion restricted to the neural pathway. Where

Table I.

RECRUITING		NON RECRUITING
Ménière's	(Most)	Conductive Losses
Labyrinthosis	(Post Fenest.)	Presbycusis (Many)
Stimulation Deafness	(Temporary)	Acoustic Neuroma
Acoustic Trauma	(Some)	Psychogenic Deafness

pathology exists in both the organ of Corti and neural pathway, it is felt that recruitment will probably be present if the proportion of hair cell damage is greater than nerve fiber involvement. If this proportion is reversed, however, then recruitment may not be present. Consequently, the presence of recruitment suggests pathology in the organ of Corti, but its absence does not preclude such pathology.

Despite the lack of rigid pathological and experimental confirmation these concepts seem to explain best the many clinical entities and to emphasize the need for further investigation.

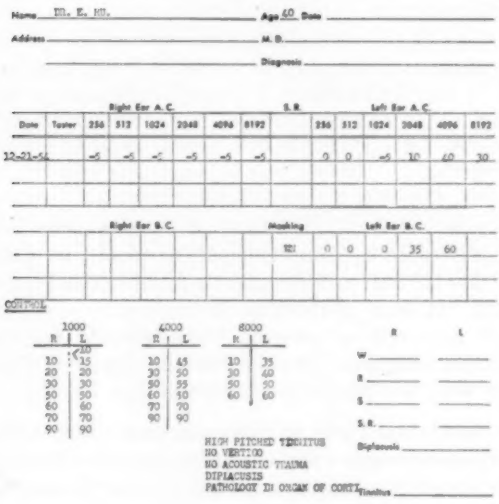
Recruitment is not present in conductive losses, acoustic neuromas, and psychogenic hearing losses. It is generally not present in presbycusis, except in certain types where the organ of Corti is primarily involved. Recruitment is characteristically present in Meniere's syndrome and post fenestration labyrinthosis; that is, until the hearing markedly improves or the pathology sufficiently extends into the neural pathways.

The use of recruitment studies to distinguish permanent acoustic trauma from presbycusis and other high tone losses has received much attention but is presently quite difficult, because recruitment may be present in only certain stages of

acoustic trauma and because many ears showing audiograms similar to those seen in acoustic trauma give no history of exposure to intense noise.

Fig. 1 and others are often diagnosed as acoustic trauma despite the absence of any exposure to intense noise and even though they are found in female patients. Are we justified

Fig. 1.



in labeling these ears hypersensitive to noise? Or is this hereditary nerve deafness; a type of labyrinthosis, or some other condition?

The next few slides show the usefulness of recruitment studies in establishing the major site of pathology.

Fig. 2 shows vertigo, etc., and the absence of recruitment indicates pathology in neural pathway.

Fig. 3 presents classical Meniere's with recruitment indicating pathology in organ of Corti.

Fig. 2.

JEFFERSON HOSPITAL
HEARING RECORD

Referred By

NAME: L. R. AGE: 47

ADDRESS: Men's Special Ward

AIR CONDUCTION

DATE	RIGHT 125	250	500	1000	2000	4000	8000	LEFT 125	250	500	1000	2000	4000	8000	CHAN.
11/26/54		25	45	65	60	75	85		10	15	30	35	50	45	
		25	45	70	65	80	80		Masked W.F. 60 db.						
		Masked W.F. 60 db.							10	15	30	35	50	35	

BONE CONDUCTION

DATE	RIGHT 250	500	1000	2000	4000	OFF EAR MASKED LEVEL	TYPE	LEFT 250	500	1000	2000	4000	CHAN.
11/26/54	30	25	45	60	75	-	-	30	20	30	40	55	
	-	50	-	-	-	80 db	WN	-	30	30	45	55	

SPEECH RECEPTION

DATE	RIGHT	LEFT	FREE FIELD	REF.	MIC	PHO	CHAN.
11/29/54	60	-	-	Sp.			

HEARING AID

DATE: NAME:
MODEL: SIZE: VOL. TONE FREE CHAN.
DO-O
DIAGRAM

DISCRIMINATION

DATE	RIGHT SCORE	LEVEL	MATERIAL	MIC	PHO	LEFT SCORE	LEVEL	MATERIAL	MIC	PHO	CHAN.
11/29/54	90%	90 db	Fb.			1% Hearing in left.					
11/29/54	46%	90 db				80 db.	WN in left.				

WORDS

DATE	RIGHT CONVER-SATION	WHISPER	NAME	SCHOOLBOOK	LEFT CONVER-SATION	WHISPER	NAME	SCHOOLBOOK

REMARKS:

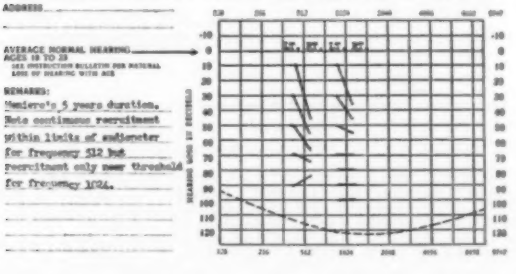
11/24/54

500		1000	
RT.	LT.	RT.	Lt.
45	15	70	30
60	30	90	45
75	45	110	75

Cold caloric shows no response on right, perverted response on left (horizontal instead of rotary nystagmus with head forward), and absence of sensitivity reactions. Operation 12/9/54 disclosed large acoustic neurom. Note absence of recruitment and poor discrimination with opposite ear masked.

FORM 102 — 1000 1-55

Fig. 3.



AUDIOGRAM OF A. Y. AGE 32 DATE 3-14-54

ADDRESS

AVERAGE NORMAL HEARING AGES 18 TO 29
SEE INSTRUCTION BULLETIN FOR NATURAL LOSS OF HEARING WITH AGE

REMARKS:
Meniere's 5 years duration.
Note continuous recruitment within limits of audiometer for frequency 512 but recruitment only near threshold for frequency 1024.

HEARING LOSS IN DECIBELS

128 256 512 1024 2048 4096 8192 CPS

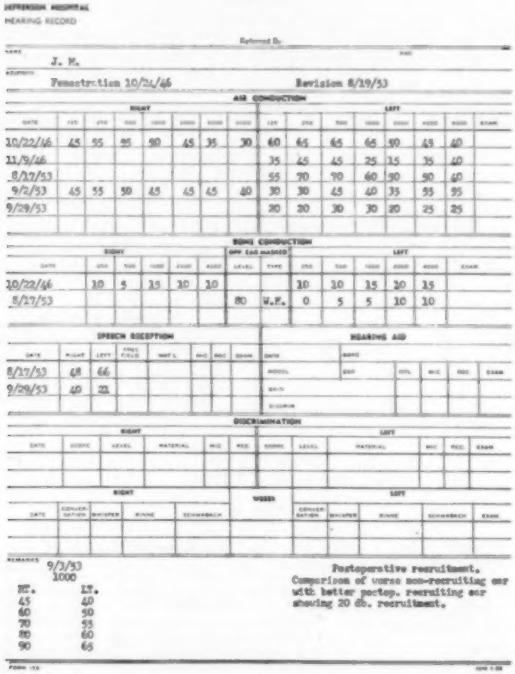
-10 0 10 20 30 40 50 60 70 80 90 100 110 120

LT. RT. LT. RT.

This last slide also helps confirm our impression that there is essentially only one type of recruitment which may vary in degree as measured by the alternate loudness balance test. Different degrees may occur in the same individual.

There is also a prognostic value to the presence of recruitment since it seems to be associated with hearing loss that is in a state of flux.

Fig. 4.



For example, as Dr. Harbert points out that in post fenestration labyrinthosis (see Fig. 4), as long as recruitment is present there is still some possibility of hearing improving or getting worse; however, once recruitment disappears there

is very little chance of improvement in hearing. The disappearance of recruitment in Meniere's syndrome without improvement in hearing often suggests neural pathology and a less favorable prognosis. These generalizations are, of course, not without exception, for they are necessarily based on limited clinical experience, but they serve as a frame of reference in which further studies and interpretation of recruitment may be evaluated.

In conclusion, the fact that recruitment of loudness is characteristically present in some conditions but not others and that it can be established by tests simple enough to perform in an otologist's office warrants its routine use in patients with perceptive hearing loss; furthermore, its presence or absence in a patient whose clinical picture is otherwise inconclusive may help localize the predominant site of pathology in the ear.

MASKING.

The ear is constantly bombarded by auditory stimuli and spontaneous aural discharges. When a stimulus is not appreciated because of the simultaneous presence of another, one stimulus is said to mask the other. The relation of ambient or masking noise to the stimulus is often compared to a field of grass (ambient noise) and a flower (stimulus). It is important to remember that the flower in this analogy need not protrude above the level of the grass. It can be appreciated even when it is a certain distance below the surface. For the important speech frequencies white noise masks at a level of about 30 db below its overall level. In other words, the flower is appreciated at a level 30 db below the surface of the noise level. In the case of low tones (below 300) the level is 45-65 db below the overall level. This is one reason for the difficulty of eliminating low tone hearing by masking.

Clinical application of the above is that the ambient noise in a test room should not be above 30 db for free field testing. If both ears are covered by doughnut receivers there is attenuation of ambient noise of 20 db (10 for low and 30 for high frequencies). A room with 50 db noise level is, therefore suitable for pure tone and speech audiometry when phones are

used. The above applies to testing normal ears. For pathological ears, a higher noise level is quite satisfactory. It is important, however, not to check calibration of an audiometer on normal subjects in a room with higher noise levels.

AIR CONDUCTION.

In order to test one ear it is often necessary to eliminate the other during the test. This is accomplished by masking on the principle that when the neural pathways of one ear are occupied by stimuli, a lesser stimulus from the other cannot be perceived. When the stimulus is presented to one ear by ear phones there is a physiological interaction between the two

Fig. 5.

JEFFERSON HOSPITAL
HEARING RECORD

Referred By

NAME W. W. L. AGE

ADDRESS

AIR CONDUCTION

	RIGHT							LEFT						
DATE	125	250	500	1000	2000	4000	8000	125	250	500	1000	2000	4000	8000	EXAM
12/26/51	45	55	55	55	40	50	45	45	50	55	55	35	40	40	Precp.
9/3/52	65	70	80	70	80	80	-	45	45	55	50	35	50	50	Postop

BONE CONDUCTION

	RIGHT						OPP EAR MASKED		LEFT						
DATE	250	500	1000	2000	4000	LEVEL	TYPE	250	500	1000	2000	4000	EXAM
11/4/52	5	10	10	30	30	No Mask.		-5	-5	5	30	30	
	5	10	10	35	30	80	W.F.	-5	-5	0	30	25	
	20	30	20	40	35	100	W.F.	0	10	20	30	30	

SPEECH RECEPTION

DATE	RIGHT	LEFT	FREE FIELD	MAT'L	MIC	REC	EXAM
12/26/51	46	43		Sp.	X		
6/5/52	60	42		Sp.	X		
7/28/52	66	43		Sp.	X		

HEARING AID

DATE	MAKE	MODEL	EAR	RTL	MIC	REC	EXAM
		GAIN					
		DISCRIM					

DISCRIMINATION

	RIGHT						LEFT					
DATE	SCORE	LEVEL	MATERIAL	MIC	REC	EXAM	SCORE	LEVEL	MATERIAL	MIC	REC	EXAM
10/30/52	86%	100 db	Ph.	X			96%	90	Ph.	X		
11/4/52	6%	100 db	Ph.	X			Masked at 90 db.					

WEBER

	RIGHT					LEFT				
DATE	CONDUCTION	WHISPER	RINNE	SCHWABACH	EXAM	CONDUCTION	WHISPER	RINNE	SCHWABACH	EXAM

REMARKS

Otosclerosis with unsuccessful fenestration right ear.
Cold caloric test gives no response from right ear.
Note apparently good hearing in dead right ear even by bone conduction with masking and unmasked speech reception.

FORM 150 10M 7-52

ears. This interaction is small, amounting to about 5 db of masking or attenuation. There is also a transmission of some

of the signal energy to the opposite ear. It has been shown that the attenuation across the head is about 40 db for low tones (200-300). 55 db for middle frequencies and 60 db for higher frequencies.[1]

The ease with which low frequencies cross the skull is another reason for the difficulty in masking low tones. It is apparent, therefore, that whenever there is a difference of 50 db or more between the two ears, masking is necessary to eliminate the possibility of a shadow curve from the better ear. To be certain of eliminating crossed hearing, a good rule is to mask for differences of 40 db or more. Stimuli from one ear reach the other by air conduction around the head, through the headband, and by bone conduction. Of these bone conduction is the most important.

Table II.

MAXIMUM LOSS MEASURABLE BY AIR CONDUCTION FOR SPEECH FREQUENCIES.

RIGHT NORMAL EAR	COMPLETE LEFT PERCEPTIVE DEAFNESS
80 db white noise mask produces about 50 db masking. (30 db ineffective).	110 db air conduction loss (60 db loss across head plus 50 db loss due to masking).
RIGHT EAR WITH 50 db PERCEPTIVE LOSS	COMPLETE LEFT PERCEPTIVE DEAFNESS
80 db mask produces no masking (30 db ineffective) (50 db not heard).	110 db air conduction loss (60 db loss across head plus 50 db loss due to perceptive lesion).
RIGHT EAR WITH 50 db CONDUCTIVE LOSS	COMPLETE LEFT PERCEPTIVE DEAFNESS
80 db mask produces no masking (30 db ineffective) (50 db not heard).	60 db air conduction loss (loss across head).
100 db mask produces 20 db masking.	80 db air conduction loss.
120 db mask produces 40 db masking.	100 db air conduction loss.

80 db is the maximum intensity of masking that can be used in the opposite ear without stimulating the tested ear, because 50 to 60 db does not cross over, due to the attenuation across the head, and the first 30 db that do are ineffective for masking. This is also the maximum level that most patients

will tolerate comfortably. It is important to recognize the importance of the type of hearing loss present in the masked ear to assess the amount of masking produced (see Table II and Fig. 5).

The degree of hearing loss measurable by masking the opposite ear is obtained by assessing the total perceptive loss of the masked ear under conditions of masking and adding the attenuation across the head. In air conduction measurements, the attenuation across the head is about 60 db for the speech frequencies (5 db physiological interaural masking plus 55 db attenuation). In bone conduction measurements, the attenuation is only a few db. The effectiveness of masking will vary with the type and degree of hearing loss in the masked ear, as well as the type of masking sound used (see Table III).

Table III.

MAXIMUM BONE CONDUCTION LOSS MEASURABLE FOR SPEECH FREQUENCIES.

NORMAL RIGHT EAR	COMPLETE LEFT PERCEPTIVE LOSS
80 db mask produces 50 db masking (30 db ineffective).	55-60 db bone conduction loss (loss 5-10 db across head).
RIGHT EAR WITH 50 db PERCEPTIVE LOSS	COMPLETE LEFT PERCEPTIVE LOSS
80 db mask produces no masking (30 db ineffective) (50 db not heard).	55-60 db bone conduction loss.
RIGHT EAR WITH 50 db CONDUCTIVE LOSS	COMPLETE LEFT PERCEPTIVE LOSS
80 db white noise produces no masking (30 db ineffective) (50 db not heard). 100 db mask produces 20 db masking. 120 db mask produces 40 db masking.	5-10 db bone conduction loss (loss 5-10 db across head). 25-30 db bone conduction loss. 45-50 db bone conduction loss.

For white noise, the effective masking is roughly 30 db below the overall noise level. With the complex low tone masking noise on many audiometers there is often great variation in its effect on different frequencies. The following examples refer to white noise masking. Clinicians are aware of the necessity of masking when doing pure tone audiometry. Its role in speech audiometry is often neglected (see Figs. 2 and 5).

CONCLUSIONS.

Whenever there is a difference of 40-50 db between a normal and pathological ear, it is necessary to mask the better ear to eliminate crossed hearing. This applies to speech audiometry as well as pure tone.

The degree of hearing loss measurable by masking the opposite ear is obtained by assessing the total perceptive loss of the masked ear and adding the attenuation across the head. In air conduction measurements, the attenuation across the head is about 60 db for the speech frequencies (5 db physiological interaural masking plus 55 db attenuation). In bone conduction measurements the attenuation is only a few decibels. The perceptive loss is assessed on the basis of residual bone conduction in the masked ear under conditions of masking.

Eighty db of masking, preferably by white noise, is tolerated by normal ears and does not overmask.

Bone conduction should always be done with masking. Otherwise, we are testing only the better ear, regardless of where the oscillator is applied.

The difficulty of eliminating crossed hearing in bone conduction measurements by masking an ear with a conductive loss casts doubt on the validity of bone conduction measurements as usually practiced in evaluating suitability for fenestration (see Fig. 5).

REFERENCE.

1. Zwislocki, J.: Acoustic Attenuation Between the Ears. *Jour. Acoust. Soc. Amer.*, 25:752-759, July, 1953.

EXPERIMENTAL APPROACH TO THE STUDY OF THE COMMON COLD.*

ROBERT S. GOHD, Ph.D. (by Invitation),
Boston, Mass.

Approximately two years ago our laboratory was set up for the purpose of studying viruses attacking the upper respiratory tract. The most common of these viruses with which we are working and the one that has most successfully resisted study, is the cold virus. The difficulties, simply put, are problems of diagnosis, of isolation, and of culture.

There is no simple, easy way of distinguishing an acute rhinitis of viral etiology from other disorders producing essentially similar clinical symptoms.[1] The situation is similar with respect to the cultivation of common cold virus under laboratory conditions. Attempts to establish this virus in experimental animals, other than the chimpanzee, has not been satisfactorily accomplished; therefore, it has been necessary to employ human beings for experimental purposes. Experiments with this species is expensive, requires a large medical staff, is exceedingly difficult to control, to say nothing of difficulties encountered in obtaining people for such studies.

Andrews,[2] of England, has stated his belief, and it is ours also, that the future of cold research lies in the development of laboratory procedures that will facilitate the investigation of colds. These problems inherent in studies of the cold have thus defined our task and long range objectives: that of establishing criteria for the diagnosis of cold infection and development of techniques for its study in the laboratory.

Neither of these objectives has been attained in our laboratory; however in the pursuit of these objectives a few observations quite unrelated to the immediate problem have been made which I consider to be of at least potential importance. For example, in tissue cultures it was found that cal-

* Read by invitation at the meeting of the Eastern Section, American Laryngological, Rhinological and Otological Society, Inc., Philadelphia, Pa., January 7, 1955.

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cium was an essential requirement for the growth of influenza virus.[3] By precipitating calcium inside the cells with phosphate, or by binding calcium in a soluble complex with a strong chelating agent, growth of influenza was prevented. The addition of calcium to the system completely reversed the inhibition in a specific manner and permitted the normal proliferation of influenza.

Another observation was that some adenoid tissues from apparently normal individuals contain what we prefer to call an epithelium stimulation factor.

Our problem, in reality is actually two problems: the first is growing the virus under laboratory conditions; the second and more important problem is finding some simple, easily observed manifestation of virus activity to indicate its growth and its presence.

There are a few reports in the literature indicating that cold virus was grown in tissue culture or some other laboratory medium; however, no changes were detected in the infected tissues, the tissue appeared similar in most respects to normal, uninfected tissues, and the demonstration of viral activity once again required the inoculation of human volunteers.[4,5] Thus, the tools which would facilitate the study were not supplied, and the problem remained much as before in a static condition.

On the basis of these observations, and because of the rather benign nature of the cold, we have adopted the philosophy that the cold virus possibly exerts its effect in a manner more subtle than the pathogenic viruses. Since gross effects as cellular necrosis and cellular inclusions do not appear to play a part in the pathogenesis of the cold virus, it seemed possible that the virus affects the intimate processes of the cell, such as multiplication and metabolism. What we are searching for is a single reproducible effect of the virus.

In view of recent successes attained with the polio virus, the methods of tissue culture are being exploited in our laboratory. The polio virus destroys fibroblasts from a variety of tissues employed in cultures. Unfortunately, the cold virus has no such effect, destroying neither fibroblasts nor any other

cells that have been challenged with the virus. At the present time, the effect of virus on the metabolism of host cells in tissue culture is also being examined.

It has seemed to us that many of the ordinary methods for studying viruses have been attempted with the cold virus; therefore in our search for the elusive effect, we do not hesitate to employ unusual or exotic procedures if there is even a remote rationale for such a procedure, and this reasoning led us to the series of experiments that employed adenoid tissue.

One approach for growing viruses that cannot infect ordinary laboratory animals, or media, is to graft a tissue from the susceptible host to the ordinarily nonsusceptible laboratory subject and then infect the grafted tissue with virus. There are two reports on the successful cultivation of Herpes zoster employing the technique with human skin.[6,7]

This approach was also employed in our laboratory. Adenoids that were obtained at the Eye and Ear Operating rooms from ostensibly normal individuals were grafted to the chorioallantoic membrane of fertile eggs incubated for 11 to 12 days. The purpose of the experiment was to provide a tissue system, that eventually would be challenged with the cold virus, and then examined for pathologic alterations of the tissue. The actual challenge of the graft with virus was uneventful; however, normal grafts independent of virus, produced such striking changes in the embryonic membrane that it seemed of importance to determine the nature of the phenomenon.

The schematic diagram in Fig. 1 is a cross section of fertile egg incubated 12 to 15 days. The structure that is important in the grafting procedure is the chorioallantoic membrane. This thin membrane contains two single layers of epithelium, one adjacent to the shell and one layer facing the allantoic fluid (see Fig. 2). The membrane is highly vascularized and is the functioning respiratory organ of the developing embryo. There is paper-like membrane between the shell and the chorioallantoic membrane, and it is necessary to separate these two structures before grafting. This is accomplished by dropped

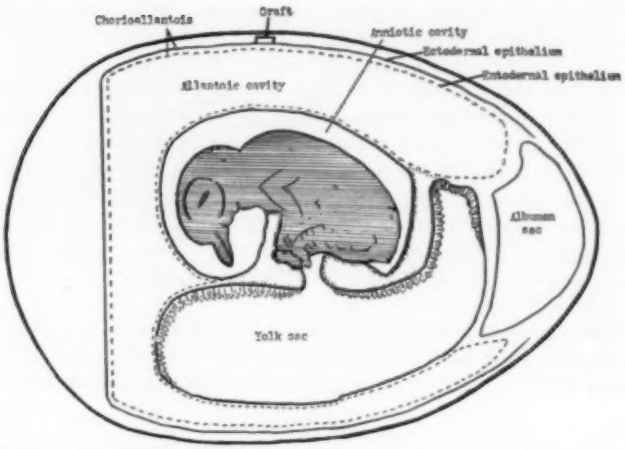

Fig. 1. Diagrammatic sketch of 12-15-day chick embryo. The site of the graft and the two epithelia of the chorioallantoic membrane are indicated.

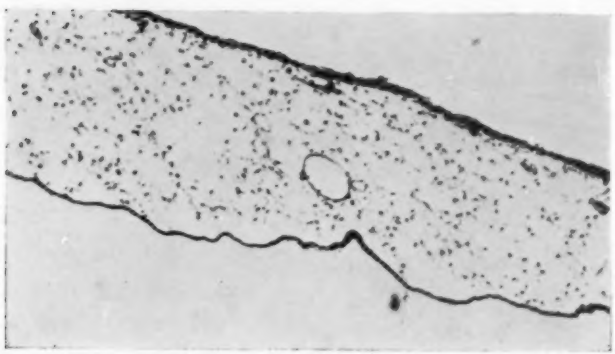

Fig. 2. Section of normal chorioallantoic membrane from chick embryo incubated 13 days. The membrane consists of a squamous epithelium (bottom) a single layer of cells that lines the allantoic cavity, a middle layer of loose connective tissue that contains blood vessels, and a cuboidal epithelium severals in depth that is in contact with shell membrane (top) x 100.

membrane technique. A small hole is made in the shell at the air sac and also in the middle.

Sucking the air out of the air sac end creates a false air sac at the middle and separates the allantoic membrane from the shell. It is then an easy matter to chip away a circle of shell about 2 cm. in diameter without damaging the underlying structures. A small piece of adenoid tissue is then put through the defect in the shell and placed directly on the chorioallantoic membrane. The defect is covered with Scotch tape and the egg put back into the incubator.

Evidence of grafting was apparent after 24 hours, and firm attachment took place within 48 hours. This was evident microscopically by the disappearance of chick epithelium that is

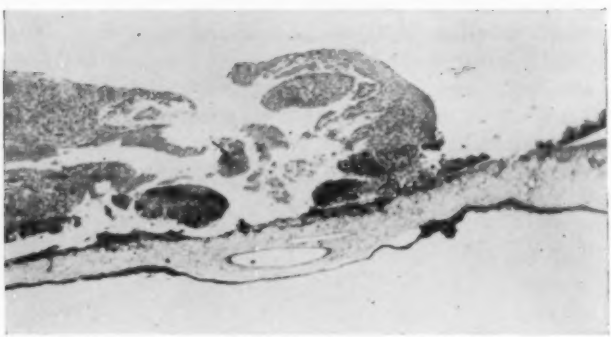

Fig. 3. Segment of normal human adenoid grafted to chorioallantoic membrane of 12-day chick embryo. After 48 hours, portions of the squamous epithelium on the side distal to the graft have formed papillae and are now multilayered x 50. The adenoid frequently is torn loose in the process of sectioning 48-hour grafts.

in direct contact with the graft and by the invasion of the graft by chick fibroblasts. A most striking change occurred in the epithelium of entodermal origin, that is the epithelium that was not in contact with the graft but distal to it (see Figs. 3, 4, 5).

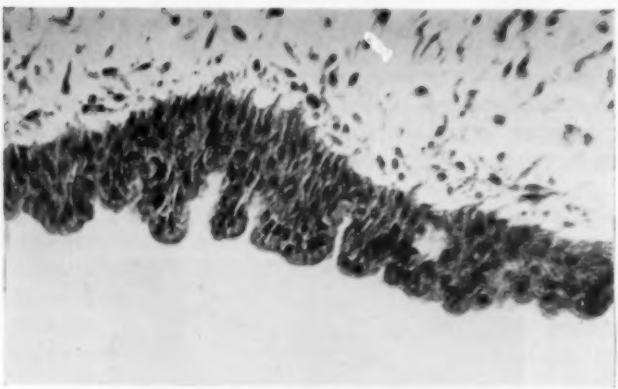

Fig. 4. Entodermal epithelium of 14-day chick embryo, 48 hours after the grafting of normal adenoid to chorioallantoic membrane. The epithelium is papilliform and contains several layers of cells x 430.

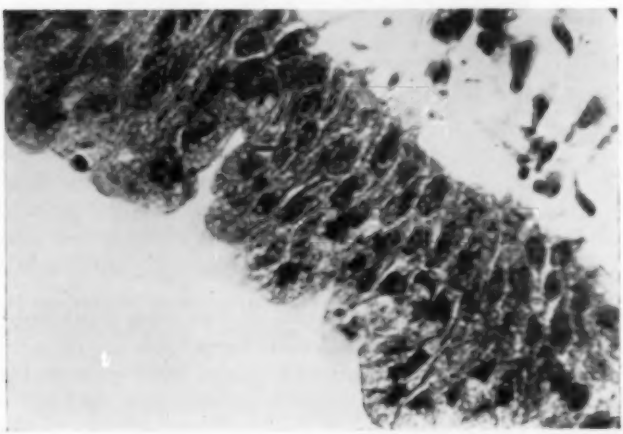

Fig. 5. Entodermal epithelium of 14-day chick embryo, 48 hours after the grafting of normal adenoid to chorioallantoic membrane. The epithelium is papilliform and contains several layers of cells x 970.

These are the cells that line the allantoic cavity. Hyperplasia and metaplasia were observed. The character of the epithelium changed from a thin single layer squamous epithelium to a wildly growing multilayered columnar epithelium. On occasion portions of the epithelium appeared undifferentiated, losing its epithelial nature and in some respects resembling tumor tissue (see Fig. 6).

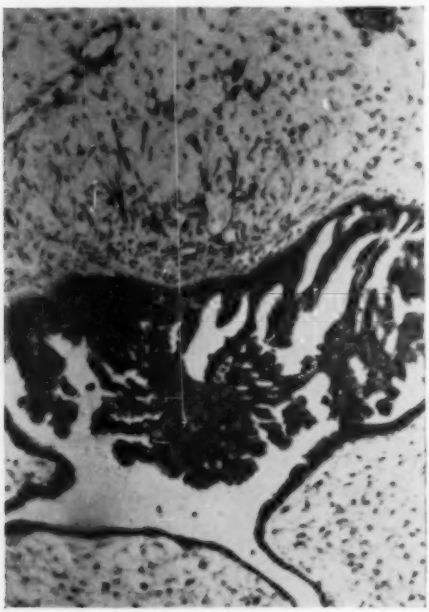

Fig. 6. Entodermal epithelium from embryo incubated 15 days and three days after the grafting procedure. The chorioallantoic membrane has invaginated. Portions of the entoderm has lost its epithelial character and has formed a growth that resembles tumor tissue x 100.

As early as 24 hours after the placement of the adenoid, proliferation of the entoderm could be detected. The epithelium increased in height and in concentration of cells and reached a maximum at 48 to 72 hours. Degenerative changes

were observed at 96 hours. The epithelium apparently became friable, and portions of it were frequently sluffed. Sections made at this time showed patches of membrane without epithelium.

At 96 hours and later the middle portion of the membrane became filled with increasing quantities of connective tissue. The adenoid itself underwent a considerable change, as a result of the grafting procedure. At first the lymph follicles were filled with lymphocytes. At 48 and 72 hours there was evidence that the graft was being invaded by embryonic blood vessels, and chick erythrocytes were seen in these vessels. Lymphocytes decreased in number. Ten days after grafting and a day or two before hatching the graft was highly vascularized, filled with new blood vessels and virtually devoid of lymphatic tissue.

The grafting procedure, as well as the development of the graft, proceeded without a deleterious effect on the embryos. Chicks hatched in good condition at about the same time as the controls without adenoids.

In regard to this phenomenon the following observations have been made: It was found that the method of placement of tissue was important. The adenoid tissue is generally incubated in an antibiotic solution for an hour and then it is cut into several small pieces. One piece is added to each egg. If the surface epithelium of the adenoid was placed next to the membrane, the graft did not fuse with the membrane and no stimulation of entoderm occurred. It was necessary to place a newly cut surface adjacent to membrane for a successful graft.

During the course of the work we wondered whether the increase in the number of cells of the entoderm was due to a stimulation by some soluble factor elaborated by the adenoid that diffused into the membrane, or whether it was actually the migration of adenoid cells to the entoderm. The next two experiments indicated that the apparent stimulation was not migration of cells but was caused by some soluble element, either present in the adenoid or secreted by it.

The first experiment examined the possibility of migration of cells. Adenoid tissue was incubated first in a vital stain, trypan blue, and then grafted to the chick embryo. The stain labeled the adenoid cells by dyeing them blue. The degree to which they migrated into the embryonic membrane could be observed, merely by examining sections of the membrane underlying the graft for blue stained cells.

Blue material of adenoid origin was observed in the middle or loose connective tissue area of the chorioallantoic membrane. The cells containing the stain appeared to be phagocytic cells. The nature of this experiment was such that it could not distinguish between phagocytes of adenoid origin that had migrated to the embryonic membrane and phagocytes of embryo origin that had engulfed adenoid material. The most important fact brought out by this experiment was that blue stained cells never were observed in the entodermal layer of epithelium. This indicated that the apparent stimulation of of epithelium was not caused by a migration of adenoidal cells from the graft.

A second series of experiments were performed to determine whether the intact adenoid segment was required for epithelial stimulation. Accordingly, extracts that were free of cells and tissue homogenates were prepared from adenoids. Both of these substances proved to be active; however, the stimulation induced by extracts was not as great as with the intact adenoid. These results suggested that this factor was either a small foreign substance that was present in the adenoid at time of grafting, such as a virus, or was a soluble substance elaborated by the adenoid tissue, such as a hormone or growth factor.

A serious effort was made to demonstrate a transmissible agent, that is a possible virus, since our laboratory was oriented towards virology. So far our attempts have been unsuccessful; no agent has been isolated.

The stimulation appears to be specific for adenoid. Several tissues have been tested, including tonsils and corneas of human and bovine origin. Other laboratories have employed skin and muscle in similar procedures apparently without

producing an effect on the allantoic entodermal cells. The activity does not seem to be an inherent property of lymphoid tissue, although we have not tested all sources of such tissue.

A disturbing factor that has troubled us is that all adenoids do not possess epithelial stimulation activity. Roughly, 40 to 50 per cent of all adenoids grafted were active; 90 per cent of the grafts were successful, but only about half of these produced changes in the allantoic entoderm. We do not know why adenoids from certain normal individuals possess activity and adenoids from others do not. Failures could not be correlated with the age of the donor. Epithelium stimulation was observed with adenoids from young children, adolescents and young adults. Failures could not be related to the differences of sex. Time of the year may be an influential factor. The percentage of adenoids having the stimulation factor was higher for those examined during the Winter than those for the Summer months; however, the differences may not be significant.

At the start of the adenoid phase of our investigation it seemed important to explore the phenomenon of epithelial stimulation because of its possible relationship to the cancer problem. Information regarding factors that stimulate or limit cellular growth would certainly be of value in the ultimate understanding of carcinogenesis. Carcinogenesis, vitamin, hormone and virus have been considered as the possible etiology of the epithelium stimulation.

Because the epithelium undergoes necrosis after four days and apparently never develops an invasive or malignant property, the theory of a carcinogenic activity of adenoids has been temporarily discarded. Vitamin A produces marked changes on squamous epithelium in tissue cultures, stimulating growth of the cells and changing them to columnar ciliated cells. It is also well known that certain hormones produce tremendous cyclic proliferative changes in the endometrium of the female. Both of these possibilities have been considered. The fact that homogenates and extracts of adenoid tissue are active is consistent with hormonal or vitamin stimulation; however, the sporadic behavior, that is the dif-

ferences observed between different adenoids, militates against this thesis.

Most of the observed data is consistent with a viral etiology as the cause of the epithelial stimulation. The very erratic nature of the adenoids can be accounted for on the basis that certain ones harbor a latent or masked virus. Adenoids possessing activity would be those containing virus, adenoids without activity would be devoid of virus. According to Rivers in his text, stimulation of epithelium, followed by necrosis, is consistent with the pathogenesis of virus infection of cells. This has been observed with certain animal viruses, as well as with vaccinia virus.

The production of pathology in the allantoic membrane, by employing inocula of either extracts or tissue homogenates, fortifies the virus thesis. Were it not for the fact that the transmission experiments were negative the thesis of virus etiology would be highly plausible. The results of an investigation that was reported recently may provide the answer to our negative experiments.

Huebner[8] and his associates at the National Institute of Health, and in collaboration with a group at Johns Hopkins, have been isolating viruses from the nose and throat. Over 100 strains of what they term adenoidal-pharyngeal-conjunctival agents have been isolated by them; 43 strains have been isolated from adenoid and tonsillar tissue removed surgically from normal individuals. These agents are characterized as cytopathogenic for HeLa cells in tissue culture.

A peculiar phenomenon is that the adenoid virus can not be isolated directly by culturing of these HeLa cells because it is in a "masked" form in the adenoid tissue. It is first necessary to culture the adenoid for prolonged periods in roller tubes. This unmasks the virus, and it then can readily be grown in HeLa cultures.

This report thus provides a possible explanation for our observations. Our inability to transmit epithelium stimulating agent may be due in fact to a masking mechanism similar to that reported by Huebner.

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NEW YORK EYE AND EAR INFIRMARY.

ALUMNI ASSOCIATION DINNER.

A subscription dinner honoring Edgar B. Burchell, D.Sc. on the completion of 60 years of distinguished service at the New York Eye and Ear Infirmary, will be given on June 10, 1955, at the 7th Regiment Mess, 643 Park Avenue, at 67th Street, New York City. Cocktails and reception at 6:30, dinner at 7:30 P.M. For further information write to Dr. Joseph H. Krug, Secretary-Treasurer, Alumni Association, New York Eye and Ear Infirmary, 218 Second Avenue, New York City.

SECONDARY RADICAL NECK DISSECTION.*

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Failures in the surgical management of cancer of the larynx are commonly observed as either local recurrences or as regional metastases. Local recurrences usually occur when the magnitude of the primary operation is less than total laryngectomy, *i.e.*, following any form of cordal resection, such as the laryngo-fissure operation, or the endolaryngeal resection technique. Failures following laryngectomy may occur as local recurrences but occur mostly as cervical metastases. Such metastases less frequently are the manner in which thyrotomy failures are also first manifested. Needless to say, in many instances the first indication of failure in the treatment of this malignancy is made through the identification of a remote or organ metastasis, regardless of the type of primary operation.

Recurrences within the larynx, following thyrotomy, indicate inadequate surgical resection of the primary cordal lesion.[1,2,3] Ordinarily a more radical technique, laryngectomy, is employed as the corrective measure for this type of recurrence, but it may be that a revision of the initial thyrotomy can effectively resect this lesion. Further consideration of this type of failure is not relevant to this study. It is of pertinent importance, however, to accept as fact that the detectable presence of cervical lymph nodes following operation for cancer of the larynx constitutes presumptive evidence of malignant metastases. Immediately one must appreciate the greater seriousness of this failure, as compared to local recurrence, for now the disease has extended beyond the confines of the larynx and is threatening general body dissemination. It must be understood that in such circumstance, if cure is to be obtained it can be only through wide field radical neck resection.

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The inadequacy of the primary operation, as herein referred to, is not simply a reflection of error in judgment, or of the improper selection of operation, but rather implies the presence of an undetected or undetectable microscopic metastasis at the time of operation. In like manner, it may appear that the development of regional metastasis voids the rational appraisal of the various criteria that characterize a tumor, and nullifies an operation well performed and presumably properly selected. Statistics pertaining to primary five-year cures correct this misrepresentation. Based solely on the proper appraisal of these accepted criteria, operations are correctly selected in from 70 per cent to 85 per cent of cases.[1,3,4,5]

The issue being undertaken at this time, however, is not the selection of the primary surgical procedure for cancer of the larynx but rather to discuss the fate of those individuals who do develop regional metastases following either thyrotomy or laryngectomy, and who are then subjected to secondary radical neck dissection.

The management of cervical metastases of previously operated laryngeal cancer is a complicated problem. Consideration and appraisal of the initial lesion, the primary operative procedure performed, the apparent extent of the local metastasis, and a diligent search for remote metastases must be made and evaluated in order to plan for the surgical resection of this malignant cervical mass.

THYROTOMY.

As defined in a previous report, the operation of thyrotomy should be elected in instances wherein the "carcinoma is so situated as to be entirely contained on the anterior or middle thirds of the vocal cord, without involvement of the anterior commissure or extension to the opposite cord, without subglottic extension or extension into the ventricle, and without any evidence of impairment of motility."[2] According to this definition then, properly selected cases operated by the technique of thyrotomy should, and ordinarily do, result in a reasonably high percentage of primary surgical cures.

Failures following primary thyrotomy, including both local recurrences and local metastases, are currently reported as

varying between 13 per cent and 20 per cent in large series of cases.[2,3] Local recurrences obviously are due to incomplete removal of the initial lesion. Secondary surgery in these instances, depending upon the extent of the recurrent growth, consists either of a revision thyrotomy or of a laryngectomy. Statistics relative to this type of corrective surgery are not pertinent to this issue. Local metastases, on the other hand, do not reflect on the inadequacy of the primary surgery, and although less frequent in occurrence, pose a more serious problem. Radical neck dissection, usually combined with laryngectomy, is the only surgery suitable to this contingency.

LARYNGECTOMY.

Cordal growths which fail to conform to the definition stated as acceptable for thyrotomy, and/or lesions originating on the epiglottis, the sub-glottic area, or the aryepiglottic fold, but without evidence of extension either to the lateral pharyngeal wall, the base of the tongue, or of regional or remote metastases, are suitably selected for primary laryngectomy. When we resort to laryngectomy according to this definition it, too, is accompanied in many instances by a reasonably high cure rate.

Recent statistics[4,5] report that failures following primary laryngectomy, noted as regional lymph node metastases, occur in from 20 to 30 per cent of cases, yet little is reported in the literature concerning the ultimate disposition of these patients, other than the fact that they are then subjected to either irradiation therapy or to neck resection.

Examination of these and current statistics also reveals that surgical failures following laryngectomy are of a higher incidence than are those following thyrotomy. The reason for this is apparent when one realizes that with more extensive lesions necessitating more radical primary operations, the more likely it is that metastases are present but undetectable at the time of initial operation. As applied to the clinical picture of cancer of the larynx it is apparent also that as one is obliged to advance from the operation of laryngofissure to that of laryngectomy as the initial surgical procedure, primary cures are less feasible, and the probability of regional metastases is increased.

INDICATIONS AND TECHNIQUE.

The indication for secondary radical neck dissection consists essentially of the presence of cervical metastases following operation on the larynx for carcinoma. To qualify this indication, it should be added that such cervical masses should be relatively mobile, that there be no evidence of remote metastases, that the general physical condition of the patient will tolerate such an extensive procedure and that there is no evidence of residual carcinoma within the pharynx.

STATISTICS.

The following cases of secondary radical neck dissection, 71 in number, are the cases so operated as representing this type of surgical failure selected from more than 1100 primary operations on the larynx for cancer: there were 552 cases of laryngofissure and 613 cases of laryngectomy. The 71 cases here reported do not represent the total number of failures following primary operation but only those which fitted the indications for secondary radical neck dissection as described previously.

TABLE I.

Type of Primary Operation	No.	Survived P.o. Year						Deaths
		2	3	4	5	7		
Thyrotomy	11						(63.6%)	4
Laryngectomy	60	3	2	6	24		(40.0%)	23 2 (not CA)
Laryngectomy and Block Dissection	9	1	1	2	3		(33.0%)	2
Totals	80				34		(42.5%)	31

Of the thyrotomy failures exhibiting cervical metastases, radical neck dissection was performed in 11 instances. Of these 11 patients, seven are living and well five or more years postoperatively, and four are dead of cancer. Of the laryngectomy failures similarly identified by way of palpable cervical lymph nodes, radical neck dissection was performed on 60 such patients, of whom 24 are living and well five or more

years, and 11 for less than five years following their secondary operation; 23 are dead of cancer and two of causes unrelated to cancer.

In addition to these cases, there were also operated upon nine patients with metastases occurring to the contralateral side of the neck following the procedure of one-stage laryngectomy and radical neck dissection. Of this group of nine, three are living and well for a period of five years or more and four for a period of less than five years following their second operation; two are dead of cancer.

DISCUSSION.

Secondary radical neck dissection in the treatment of cancer of the larynx is a procedure devised to salvage primary surgical failures manifesting regional metastases. In evaluating the failures so operated, of first significance is the fact that by means of this operation lives are saved. This is the primary consideration in the treatment of cancer in any part of the body. Secondarily it is also appreciated that the incidence of cervical metastases increases directly with the extent of the primary lesion.

The results to be derived from this evaluation are that first, following primary laryngectomy, cervical metastases have occurred in a relatively large percentage of instances—20 to 30 per cent. This bespeaks principally of inadequate primary surgery, thereby signifying the need and rationale for the technique of the one-stage laryngectomy with radical neck dissection. The one-stage combined operation is positively indicated wherein cervical nodes are palpable at the time of initial operation, and relatively indicated where, because of the extent or position of the carcinoma, one suspects the presence of or anticipates the early development of cervical metastases. It is only by accepting this combined procedure as a primary operative technique that the incidence of metastases following surgery for cancer of the larynx will be reduced. Second, of the failures manifesting cervical metastases which comply with the indications for secondary radical neck dissection, although a large proportion of these patients are salvaged by means of this secondary operation, more cases

would be found suitable if their metastases were diagnosed before fixation occurred. Experience has shown that surgery cannot completely resect cervical metastatic masses that are fixed to the underlying bony structures. Third, the limitations of secondary surgery to effect cure in some cases of local metastases, together with the complete inoperability of remote metastases, emphasizes the unjustifiable attitude sometimes assumed in reserving one operative procedure in the event of failure of the first procedure. The fate of such patients too often is determined long before secondary surgery is attempted.

SUMMARY.

An evaluation of the failures of primary surgery of the larynx for cancer is reported, with special consideration as to the cause of such failures.

The surgical management of cervical metastases is described, together with the results obtained in 80 cases of secondary radical neck dissection.

It is defined that secondary radical neck dissection, as a salvage procedure, is warranted and rewarding.

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255 South 17th Street.

OTITIS MEDIA—THEN AND NOW.*†

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The purpose of this paper is to compare the results of treatment of otitis media in the pre-sulfa, the sulfa and the penicillin periods, and to summarize what we think are the best methods of treatment available at the present time. The data presented are derived from our experience in the Department of Otolaryngology at the Geisinger Memorial Hospital since 1932. Table I shows the dramatic reduction in the number of mastoid operations.

TABLE I.

DECREASING INCIDENCE OF "SIMPLE" MASTOID OPERATIONS AT THE GEISINGER HOSPITAL.

Year	Period	No. Cases *Acute* Otitis Media and Mastoiditis	No. "Simple" Mastoid Operations	Per Cent Requiring Mastoidectomy
1937	Pre-sulfa	202	119	58.9
1943	Sulfa	282	74	26.2
1946	Small dose penicillin	247	10	4.0
1949	Large dose penicillin	189	5	2.7
1950	(1–3 million units daily)	158	9	5.7
1951	(1–3 million units daily)	109	1	0.9
1952	(1-3 million units daily)	110	3	2.7
1953	Larger dose penicillin	122	0	0
1954	(5–10 million units daily)	65	2	3.0

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Someone may possibly comment that the percentage of mastoid operations in the earlier years was much too high. I do not think this comment is valid, because my indications for mastoidectomy have remained the same. This series does not include acute exacerbations of chronic mastoiditis nor does it include radical or modified radical mastoid operations. During the past four years we have done 81 radical and 28 modified radical mastoid operations. I think the comparison over a period of years is valid, because these patients came from a stable community. They came to the hospital because their symptoms had not been cleared up with the methods and drugs utilized by the family physician. In each period the family physician had at his disposal the same drugs which were available to us, but in most instances the drugs were used in smaller doses and for too short a period of time.

Over this period of 18 years the number of patients admitted to our service for *all* types of disease has slowly *increased* until 1954, when over 1,000 patients were admitted to this service. This was 8.5 per cent of all hospital admissions. The decreased number of patients admitted during the last four years for treatment of acute otitis media and mastoiditis would seem to be evidence that the family physician is curing a higher percentage of these patients than he did during the preceding years.

TABLE II.

DEATHS FROM COMPLICATIONS OF OTITIS MEDIA—
PRE-SULFA PERIOD.

1932	Septicemia (1), Meningitis (3)	4
1933	Meningitis	3
1934	Meningitis	1
1935	Septicemia	1
1936	Meningitis (3), Nephritis (1)	4
1937	Brain abscess	1
1938	Meningitis (2), Brain abscess (1)	3
7 years		Deaths 17

Average number of admissions per year—737

Tables II, III and IV show the decreasing death rate from the complications of otitis media. Note that since 1950 there have been no deaths. Since 1946 I have not used the sulfona-

mide drugs except for patients with meningitis; therefore our low mortality rate since that time can properly be attributed to the judicious use of penicillin.

TABLE III.

DEATHS FROM COMPLICATIONS OF OTITIS MEDIA—SULFA PERIOD.

1939	Meningitis	2
1940	Meningitis	1
1941	Meningitis	1
1942		0
1943		0
1944		0
6 years		Deaths 4

Average number of admissions per year—721

TABLE IV.

DEATHS FROM COMPLICATIONS OF OTITIS MEDIA—PENICILLIN PERIOD.

1945	Meningitis	1
1946		0
1947		0
1948		0
1949		0
1950	Meningitis (1), Brain abscess (1)	2
1951 – 1954		0
10 years		Deaths 3

Average number of admissions per year—948

The fact that penicillin is superior to the sulfonamide drugs was also well demonstrated by Wilcox.[5] Of the 247 patients with acute otitis or mastoiditis in Wilcox's 1945-1946 series, 118 were first treated with sulfadiazine, because at that time penicillin was comparatively expensive. In 42 per cent of these cases, use of sulfadiazine was discontinued, and penicillin was administered either because the infection failed to improve or because signs of sulfonamide intolerance developed. It is surprising that the results of penicillin therapy were good, as judged by 1945-1946 standards, because only 20,000 to 50,000 units were given intramuscularly every three hours; however, that was in the days before many organisms had become relatively resistant to the action of penicillin.

Davis and McDermott[1] state: "The introduction of more potent and less toxic agents has relegated the sulfonamides to the role of drugs useful in only specialized situations."

House[3] in 1946 presented an interesting comparison of the results of treatment of otitis media before and during the sulfonamide period. In his 1935, or pre-sulfa series, 45.9 per cent of the patients required simple mastoidectomy. In his 1943 series of cases, treated with one of the sulfonamide drugs, 17.6 per cent of the patients required simple mastoidectomy.

It should be realized that acute otitis media and acute mastoiditis are not two separate and distinct processes. There is some degree of mastoiditis with every otitis media which has persisted for more than three or four days. If this mental picture were firmly planted in the minds of all physicians treating otitis media I think there would be less tendency to delay early myringotomy and early administration of one of the antibiotics.

Rutherford[4] makes some biting but well-founded comments as follows: "The complacent acceptance of the antibiotics as a cure-all in acute otitis media has led to a state where the younger pediatricians do not know the art of cleansing the ear canal, of observing and recognizing the changes in the tympanic membrane which indicate pathologic conditions in the middle ear, or how to do a myringotomy." "In fact, some of these young men and women have been taught that myringotomy is not only an unnecessary procedure but also one to be avoided because it injures and scars the tympanic membrane, although spontaneous rupture of the drum under antibiotic therapy apparently is not considered harmful. They do not differentiate between suppurative and non-suppurative acute otitis media."

The obvious answer is that otitis media should be treated only by those physicians who have the manual skill to cleanse the canal adequately and to determine by use of the *pneumatic ostoscope* whether or not there is fluid in the middle ear. In my opinion fluid in the middle ear, whether it is suppurative or non-suppurative, should *always* be evacuated by myringotomy and aspiration. I think following myringotomy the exudate in the middle ear should be evacuated with a small spot suction tube. I prefer a glass tube because it shows me

the character and quantity of fluid removed. It also furnishes a reliable sample of exudate for smears and cultures.

Rutherford[4] also states: "Natural immunity may not be acquired when drugs are used and the organisms may regain their former activity when the drug is discontinued." This in my opinion is a theoretical consideration which should not deter us from early administration of penicillin. The almost complete elimination of simple mastoid operations all over the country since the introduction of penicillin would seem to be sufficient evidence to warrant continuation of its use.

It seems pointless to argue whether use of penicillin is superior to use of myringotomy or vice versa. The sensible attitude is to employ *both* measures as soon as the diagnosis is made. During the last ten years I have not had to perform a mastoidectomy for any patient who came to me for initial treatment of the otitis media.

Men in our department have done only six simple mastoid operations during the past four years. The indication for operation in four cases was subperiosteal abscess, in one case facial paralysis and in one case meningitis. The history of each case indicated that myringotomy had *not* been performed and that penicillin had *not* been used or, if used, was given in small dose. That brings up the question of what *is* an adequate dose of penicillin. Obviously, natural resistance plays a major role in control of all infections, and if resistance is good relatively small doses of any antibiotic *may be* effective.

The *site* of the infection as well as the degree of penicillin sensitivity of the infecting organism must be taken into account in determining the size of the daily dose and the duration of treatment. There is something about infections in bone-surrounded cavities which makes them respond poorly and slowly to average doses of penicillin. Probably it is the fact that inflammatory swelling of soft tissues surrounded by bone constricts the blood supply to these tissues.

I agree with Eagle[2] and associates, who suggest that "A large dose may promote the penetration of penicillin into walled-off foci of infection, which are only slowly equili-

brated with the tissue fluids, and into which penicillin might not diffuse in adequate concentration after a small dose which provides a low head of pressure for a relatively brief period." It is with this thought in mind that I have used fortified procaine penicillin ever since it has been available, and our results have been so gratifying that I shall continue its use.

A common but frequently ineffectual program is one injection of penicillin followed by penicillin by mouth for three or four days. Only one-fifth of the penicillin taken by mouth is absorbed, so it seems rather foolish to rely on this mode of administration. We see many patients who have not been cured by small doses, but who do respond promptly to three or five million units of fortified procaine penicillin daily if this dose is continued for five to eight days.

In reviewing the charts of our last 25 patients I find that we usually give 3,000,000 units daily for children under six years of age and 5,000,000 units daily for those over six years of age. Some of the adults were given 10,000,000 units daily because they had mastoid tenderness. Several who had marked tenderness and edema over the mastoid process were cured without operation. Two of these 25 patients had infections due to a staphylococcus which grew on the five-unit penicillin plate, so they were treated with erythromycin 2 Gm. daily for a period of seven days, with prompt resolution of the infection.

Incomplete resolution can be determined if one uses a pneumatic otoscope. Impaired mobility of the drum is an indication for repeated myringotomy and *aspiration* of the exudate in the middle ear. The so-called "masking effect" of the antibiotics is no problem for the man who is experienced in the use of these procedures. A normal audiogram is additional evidence of a normal middle ear.

In order to diminish the tendency for emergence of resistant strains it is desirable to prescribe from the outset a dose schedule sufficient to insure maintenance of an optimum concentration of the antibiotic in the body fluids until clinical symptoms of the infection subside. After the symptoms have subsided, it is advisable to continue use of the antibiotic for

a period of 48 hours and then discontinue its use without a tapering off period. Only two of the 25 patients required 5,000,000 units a day for as long as 12 days.

Regardless of all that has been said about the value of *in vitro* sensitivity tests, the really dependable means of assessing the effect of an antibiotic in a given case is the therapeutic response. It is a fairly reliable rule that if an adequate amount of the right antibiotic is adminstered, marked clinical improvement will be evident within 48 hours. If such is not the case, *in vitro* sensitivity tests should be made if they have not already been done.

I have used tetracycline for a few patients, but not enough to be confident that it is as effective as penicillin for the average patient with otitis media and early mastoiditis. Most cases of otitis media are due to one of the Gram positive cocci, and in our experience, penicillin if given in large enough dose and by intramuscular injection, is still the drug of choice for treatment of most of these infections. If the *in vitro* sensitivity tests show that the organism is a staphylococcus which grows on the five-unit penicillin plate, I then use erythromycin.

A review of the charts of 25 children with acute otitis media showed that 76 per cent had an enlarged adenoid. This fact coupled with the histories of children whose repeated attacks of otitis media ceased following adenoidectomy indicates than an enlarged adenoid is one of the factors predisposing its owner to the development of otitis media. Thirty-two per cent of these 25 also had the allergic or atopic constitution. This, I believe, is another of the factors predisposing to the development of otitis media, because 10 per cent is the incidence of the allergic constitution in the general population.

For a long time I have been skeptical about the effectiveness of glycerine ear drops, because I have seen so many patients who were not cured by their use. The highly colored advertisements which we all receive frequently imply that the "highest specific gravity glycerine" will extract fluid from

the middle ear through an intact drum by osmotic action. To test the validity of this idea last summer my son and I used three anesthetized cats as experimental animals.

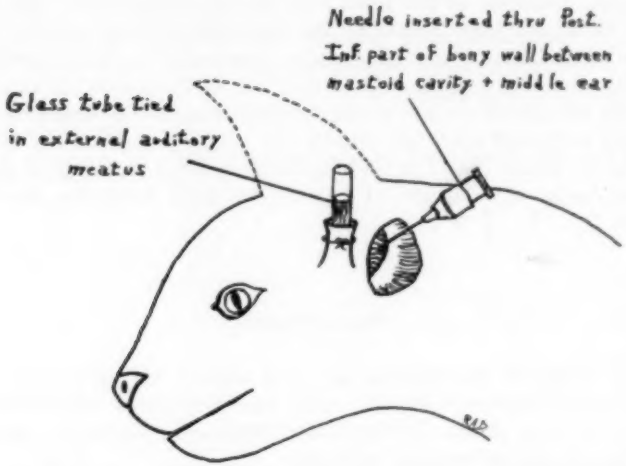

Fig. 1. The glass tube in the external auditory canal contains glycerine. The middle ear was filled with colored normal salt solution by injecting it as shown in the diagram.

Using the same illumination and magnification one does for a mastoid operation in the human, we removed the mastoid cortex and with a hypodermic needle injected normal salt solution colored with methylene blue into the middle ear through the thin plate of bone separating the mastoid cavity from the middle ear. The blue-tinted fluid was clearly visible through the translucent drum, and we could thus be certain that there were no air bubbles preventing intimate contact between the fluid and medial surface of the drum. The auricle was removed, and a snugly fitting glass tube was inserted into the external ear canal. The "cuff" of the membranous canal was tied with a purse string suture to insure a watertight joint. The "highest specific gravity" glycerine was used to fill the external ear canal and the glass tube inserted into

it. The height of the glycerine column was measured at that time and then one hour later.

In each of the three experiments the fluid column rose only 2 mm. during a period of one hour. After measuring the internal diameter of the glass tube we calculated that 0.014 cc. of fluid had been added to the glycerine already present in the external canal and glass tube. Some of this fluid undoubtedly came through the drum because in two cases, after one hour the glycerine had a slight bluish tinge. The quantity of fluid extracted from the middle ear over a period of one hour was so small that I would hesitate to recommend glycerine ear drops as a means of evacuating fluid from the middle ear.

CONCLUSIONS.

1. Surgical mastoiditis can and should be prevented by early myringotomy and by early and continuous administration of large doses of one of the antibiotics, perferably penicillin by intramuscular injection.

2. The effective dose is usually 3,000,000 to 5,000,000 units daily, but some cases may require as much as 10,000,000 units daily.

3. Use of the antibiotics should be continued until the appearance and mobility of the drum are normal, usually five to eight days.

4. Recurrence of exudate in the middle ear requires repeated myringotomy and aspiration, using a spot suction tube.

5. Glycerine ear drops are a very poor substitute for myringotomy and aspiration.

6. The incidence of acute otitis media is higher in children having an enlarged adenoid.

7. The incidence of acute otitis media is higher in children having the allergic or atopic constitution.

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CORRECTION.

In the paper "The Control of Post Operative Bleeding with Adrenosem" by Dr. Capers B. Owings, published in THE LARYNGOSCOPE for January, 1955, an error appears. On page 23, the paragraph "Adrenosem has shown, etc." should read: Adrenosem has shown no cumulative effect on human subjects treated for over two years and no toxic effects attributable to the drug. There is a high index of therapeutic safety at the usual dosage levels, and there seem to be *no* contraindications . . . . . "

This also applies to the reprints of the paper.

SINUS DISEASE AND ASTHMA: THE PROBLEM OF FOCI OF INFECTION*†

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INTRODUCTION

The relationship of sinus disease to systemic diseases has been a troublesome and confusing problem; in fact, the entire concept of foci of infection[1] of the upper respiratory tract has been questioned often by internists and pediatricians. The reason for this changing viewpoint must be that the results of therapy have been unfavorable. It is our opinion that rhinologists have been largely responsible for much of this confusion. We think that rhinologists in the past have considered upper respiratory disease too frequently as foci of infection, when no real infectious process existed.

Four years ago, a clinical research unit, including an allergist and a bacteriologist, was formed in the Department of Otolaryngology at The Mount Sinai Hospital to study particularly the relationship of nasal and sinus disease to systemic diseases. This group functioned in a special clinic one morning a week for three years. The purpose of this study was to use precise and bacteriologically valid criteria of infection as offered by Goldman [2a-b] to determine the presence or absence of infection.

In this paper we shall present our findings in bronchial asthma, which was the largest group of cases studied. We shall try to show

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that only the systematic application of definite criteria of infection to nasal and sinus disease can lead to a logical understanding and clarification of the problem.

It should be pointed out that the gross character of the secretion in the nose or obtained from a sinus, regardless of amount, color or consistency, is no index of the presence or absence of infection. Copious, thick, yellow secretion can be the manifestation of an active vasomotor rhinitis or sinusitis while scant, thin, mucoid secretion can show evidence of active and virulent infection; also, it should not be assumed that alterations in the mucous membrane of a sinus necessarily indicate infection.

True infection implies not only the presence of micro-organisms but also their active multiplication. It also should be stated that infection always begins on the surface of the mucous membrane and invades the deeper tissues in instances where it becomes uncontrolled and causes necrosis of the mucosa.

It is necessary to define the terms pathogenic, potentially pathogenic and non-pathogenic micro-organisms. Diplococcus pneumoniae, streptococcus hemolyticus, hemophilus influenzae and parainfluenzae, and klebsiella pneumoniae are considered pathogenic, even when isolated in small numbers from nasal or sinus secretion. Staphylococcus aureus A, streptococcus viridans, streptococcus non-hemolyticus, bacillus proteus and pseudomonas aeruginosa are potentially pathogenic, and are considered pathogenic only when found persistently or in moderate to large numbers. Staphylococcus albus, staphylococcus aureus B, diphtheroids and neisseria pharyngis are as a rule non-pathogenic.

MATERIAL AND METHODS

One hundred and nine asthmatic patients were referred to the research clinic for study of foci of infection in the nose and sinuses. It should be emphasized that most of these patients were referred because it was believed that infection in the upper respiratory tract was a causative factor in their asthma. The investigation included in most of the patients' Roentgen examination, diagnostic lavage of the maxillary antrums and sphenoid sinuses, and cultural and microscopic examination of the nasal, sinus and nasopharyngeal secretions by the method described by Goldman.

Eighty-two of the patients referred to the clinic had a complete allergic and bacteriologic study and, therefore, are included in this report. Fifty-eight patients showed no evidence of clinical sensitivity, and their skin tests were either completely negative or gave only scattered slightly positive reactions. They were, therefore, placed in the group termed 'intrinsic asthma".

Twenty-four patients showed definite clinical sensitivity, and their skin tests showed marked positive reactions. They were placed in the group termed "extrinsic asthma".

An additional study was made in a group of 16 patients with intrinsic asthma who showed thickened mucous membrane of the sinuses on X-ray examination. The membranes were removed at radical antrum operations, or by trephine biopsy. Cultural and microscopic examinations were made of the sinus secretion preoperatively. The membranes were triturated and cultured on blood agar plates and in broth. They were sectioned serially and prepared for both histological study and for demonstration of bacteria.

A follow-up study of sinus surgery in 61 asthmatic patients is included. These patients had been selected for operation because of persistent sinus disease with abnormal membrane. In one group of 30 cases, sphenoethmoidectomy and intranasal antrotomy were performed. In the second group of 31 cases, these procedures were supplemented by radical antrum operations.

OBSERVATIONS

1. Bacteriology of Sinus Secretion in Asthma.

Bacteriologic studies were made on the antral secretions of 82 patients. The secretions were sterile in 12 instances, yielded non-pathogens in 21, potential pathogens in 35, and pathogens in 14 (See Table I).

Among the intrinsic group of 58 patients, the antral secretion was sterile or showed non-pathogens in 19, yielded potential pathogens in 26 and pathogens in 13. Among the extrinsic group of 24 cases, the antral secretion showed no micro-organisms or non-pathogens in 14, potential pathogens in nine and a pathogen in one.

Based on the cultural and microscopic criteria we have established, 30 of the 82 patients showed evidence of sinus infection (See Table II). Among the 58 intrinsic cases, 25 had sinus infection and 33 were free from infection. Among the 24 extrinsic cases, five had sinus infection and 19 were free from infection.

TABLE I.

BACTERIOLOGY OF PARANASAL SINUSES IN BRONCHIAL ASTHMA

	Sterile	Non-Pathogens	Potential Pathogens	Pathogens
58 Intrinsic cases	9	10	26	13
24 Extrinsic cases	3	11	9	1
Total—82 Cases	12	21	35	14

TABLE II.

PARANASAL SINUS INFECTION IN BRONCHIAL ASTHMA

	Without Sinus Infection	With Sinus Infection
58 Intrinsic cases	33	25
24 Extrinsic cases	19	5
Total—82 Cases	52	30

In summary, infection was present in less than half of the intrinsic group and in about 20 per cent of the extrinsic group. The absence of infection in the majority of intrinsic cases is noteworthy because infection is frequently offered as the most probable causative factor in this form of bronchial asthma.

2. Long Term Bacteriologic Observations of Sinuses in Asthma.

Our study of these asthmatic patients over a three year period permitted us to obtain a long term bacteriological perspective in a number of patients, several of whom had had previous sinus surgery (See Table III). The following are illustrative:

Cases 1 and 2 demonstrate that pathogens may be isolated from the sinuses for a brief period of time and then not be recovered for months thereafter. These cases strongly suggest that such infections were transient in character. Their presence or clearing had no influence on the course of the asthma.

Case 3 illustrates the multiplicity of pathogens which may characterize the sinus flora of asthmatics. In this patient, Staph. aureus A was consistently present over a 10 month period. For a short time Pneumococcus Type 10 was found in two cultures, two weeks apart, and H. parainfluenza was isolated on another occasion. Then on four successive observations, neither of these two pathogens could be demonstrated.

In Case 4, three different pathogens were isolated at different times over a period of 22 months.

In Case 5, multiple infection of the sinuses caused by Staph. aureus A and Pneumococcus Type 25 was present for several months. Antibiotic therapy rid the sinuses permanently of the staphylococcus, but the pneumococcus persisted. Streptococcus hemolyticus then appeared briefly and for three months thereafter only non-pathogens could be found.

Case 6 shows that a persistent sinus infection can be caused by the same micro-organism over a period of two years, in this instance by Staph. aureus A. On two separate occasions, once for a period of several months, Streptococcus hemolyticus was also cultured from the sinus secretion.

These studies indicate the variety of micro-organisms that may inhabit the sinuses in a single case, and that they often may be transient rather than permanent residents. This multiplicity suggests a lack of specificity in the relation of the micro-organisms isolated to the underlying membrane pathology and to the continuing asthma. Variations in the bacterial flora of the sinuses was

TABLE III.

LONG TERM BACTERIOLOGIC OBSERVATIONS OF THE PARANASAL SINUSES IN BRONCHIAL ASTHMA

Time in Months

CASES	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
1—S.R.	o	o		x Pneumo. 10	x	o	o	o	o		o	o								Transient Infection				
2—E.M.	o	o	o		x Pneumo.-o Strep. hemolyt.		x Strep. virid.	x		o	o									Transient Infection				
3—V.M.	x Staph. aur. A.		x Pneumo. 10	x	x H. para-infl.	x	x Staph. aur. A.	x		x										Multiple Infection				
4—W.B.	o	o	x	x	x	x		x		x		x		x Strep. hemolyt.	x		x	x	x Pneumo. 11		x	x Strep. hemolyt. Multiple Infection		
5—E.F.	x Strep. viridans		x	x Pneumo. 25 Staph. aur. A.	x	o Antibiotics	o	o		x	Pneumo. 25	x	x Strep. hemolyt.	x		o	o	o		Multiple Infection				
6—E.L.	x				x		x Staphylococcus aureus A.				x				x						x			x
				x Strep. hemolyt.	x	x	x										x Strep.	x hemolyt.		Persistent and Transient Infection				

x = Pathogens or Potential Pathogens o = Nonpathogens

unaccompanied by any change in the asthmatic status. Such findings argue strongly in favor of the concept that pathogens isolated from the sinuses of asthmatics are invaders infecting abnormal membranes.

3. Correlation of Sinus Radiology with Bacteriologic Evidence of Infection.

Seventy-one patients had both complete Roentgen and bacteriologic examinations (See Table IV). In 15 cases *with* abnormal

TABLE IV.

RADIOLOGIC AND BACTERIOLOGIC FINDINGS OF PARANASAL SINUSES IN BRONCHIAL ASTHMA

Sinus X-ray Findings	Sterile	Non-Pathogens	Potential Pathogens	Pathogens
Negative X-rays 29 Cases	3	8	14	4
Positive X-rays 42 Cases	6	9	20	7
Total—71 Cases	9	17	34	11

sinus membranes, cultures of the sinus washings were sterile or yielded non-pathogens. Equally important is the fact that in 18 cases *without* abnormal sinus membranes, cultures of the sinus washings yielded potential or actual pathogens. When the cases were divided according to the presence or absence of infection of the sinuses, it was found that of 42 cases with positive X-rays, 18 showed sinus infection and 24 no infection (See Table V). Of 29 cases with negative X-rays, nine had sinus infection and 20 no infection. It, therefore, appears that thickened membrane of the

sinuses may be observed on roentgenograms in bronchial asthma without evidence of sinus infection and, conversely, sinus infection may be present without thickened membranes.

Our observations, however, do indicate that sinus infection was more frequent in cases with abnormal membrane findings. This combination of infection and thickened membrane was seen more often in intrinsic asthma than in asthma with detectable allergic factors. We wish to point out that this does not necessarily imply a causal relationship.

TABLE V.

RADIOLOGIC FINDINGS AND PARANASAL SINUS INFECTION IN BRONCHIAL ASTHMA

Sinus X-ray Findings	Without Sinus Infection	With Sinus Infection
Negative X-rays 29 Cases	20	9
Positive X-rays 42 Cases	24	18
Total—71 Cases	44	27

4. Bacteriology and Micro-pathology of Sinus Membranes.

These observations are offered tentatively, for, as a small group of cases, they serve chiefly to raise questions rather than to provide answers. In our evaluation of the bacteriology of the membranes we have relied entirely upon the blood plate cultures. Broth cultures permit no quantitative estimate of the micro-organisms present, so that information obtained from them may be misleading.

TABLE VI.
BACTERIOLOGY AND MICRO-PATHOLOGY OF PARANASAL MEMBRANE IN BRONCHIAL ASTHMA
1. Antral Membrane Removed at Operation

Case	Bacteriology		Pathology	
	Pre-operative	Membrane	Micro-organisms	Histo-pathology
1—S.A.	Sterile	Sterile	None	Infiltration with many eosinophils Edema
2—M.K.	Pseudomonas aeruginosa many colonies	Sterile	None	Same as Case 1
3—E.F.	Staphylococcus albus B. Few colonies	Staphylococcus albus B. Few Colonies	None	Same as Case 1
4—A.B.	Staphylococcus albus A. Few colonies	Staphylococcus albus A. Few Colonies	None	Same as Case 1
5—N.Z.	Pneumococcus 19 Moderate colonies Streptococcus hemolyticus Few colonies	Staphylococcus albus A. Few Colonies	Superficial necrosis with cocci. Few cocci beneath basement membrane	Same as Case 1
6—D.B.	M. catarrhalis Diphtheroids	Streptococcus viridans Moderate colonies	None	Same as Case 1
7—J.H.	Streptococcus viridans Staphylococcus aureus A. Moderate colonies	Streptococcus non-hemolyticus Moderate colonies	None	Same as Case 1
8—F.E.	Pneumococcus 19 Many colonies	Pneumococcus 19 Many colonies	Few cocci beneath basement membrane	Same as Case 1

Cultures of entire antral membranes, removed at operation in eight cases, revealed the following (See Table VI): In two cases the membranes were sterile on blood agar plates. The membrane of a third case showed only Staphylococcus albus B. Two membranes yielded only a few colonies of Staphylococcus albus A. The sixth membrane yielded moderate numbers of Streptococcus viridans.

The seventh showed Streptococcus non-hemolyticus in similar numbers. The eighth membrane yielded many colonies of Pneumococcus Type 19. In general there was agreement between preoperative cultures of sinus secretion and membrane cultures. The single discrepancy was the finding of pathogens in the secretion that were not cultured from the membrane (See Case 5).

TABLE VII.
BACTERIOLOGY AND MICRO-PATHOLOGY OF PARANASAL SINUS MEMBRANE IN BRONCHIAL ASTHMA
2. Trephine Biopsy of Antral Membrane

Case	Bacteriology		Pathology	
	Pre-trephine	Membrane	Micro-organisms	Histo-pathology
9—M.C.	Sterile	Sterile	None	Infiltration with many eosinophils Edema
10—T.B.	Sterile	Sterile	None	Same as Case 9
11—E.G.	B. Proteus many colonies	Staphylococcus albus B.	None	Same as Case 9
12—M.M.	Aerobacter Aerogenes	Aerobacter Aerogenes	None	Same as Case 9
13—C.O.	Sterile	Staphylococcus aureus A. many colonies	None	Non-specific acute and chronic inflammation
14—K.K.	B. Proteus many colonies	B. Proteus many colonies	None	Same as Case 13
15—C.R.	Streptococcus viridans Moderate colonies	Staphylococcus aureus A. many colonies	None	Same as Case 13
16—J.S.	K: Pneumoniae many colonies	Streptococcus hemolyticus moderate colonies Staphylococcus aureus A. moderate colonies	Occasional cocci in surface exudate Very few within tissue	Same as Case 13

Cultures of membrane biopsies in eight cases, obtained by trephine through the inferior meatus, revealed the following (See Table VII): The membranes in two cases were sterile, in two

others yielded only non-pathogens. Four showed many colonies of potential or actual pathogens.

Micro-pathology showed the characteristic allergic membrane in 12 of the 16 cases, namely many eosinophils, marked edema and thickening of basement membrane. Four showed acute and chronic non-specific inflammation characterized by infiltration with neutrophils, lymphocytes and plasma cells. No micro-organisms could be seen in 13 of the membranes. Of the three in which micro-organisms were seen on section, two were operative specimens with the pathologic alterations of an allergic type, and one was a biopsy with non-specific inflammation. Micro-organisms were few in all three, and in two were observed chiefly in surface exudate or localized superficial necrosis.

It is noteworthy that of the 16 membranes studied, seven showed typical allergic tissue changes despite sterile plate cultures or growth of only non-pathogens and the lack of micro-organisms on sections.

5. Follow-up Study of Sinus Surgery in Asthma.

Sixty-one cases of asthma, presumed to be associated with infectious sinus disease, had follow-up observations from one to 14 years after sinus surgery. These cases were divided into two groups: the first, a group of 31 cases, had radical spheno-ethmoidal and antral surgery, including Caldwell-Luc or crestectomy procedures (See Table VIII); the other group of 30 cases had spheno-ethmoidal surgery with simple intra-nasal antrotomies instead of radical antrum procedures (See Table IX).

The results in the first group were as follows: Six were found to have had a distinctly more favorable course after operation. Of these, two experienced prolonged arrest or "cure" of the asthma, 25 were unimproved or worse.

The postoperative rhinologic status was evaluated in 28 of the 31 cases. Polypoid regrowth was present in 12 cases and gross sinus

FOLLOW-UP STUDY OF SINUS SURGERY I
TABLE VIII. BRONCHIAL ASTHMA

1. With Radical Antrum Operation

Follow-up years	Cases	Asthma			Rhinologic Status		
		Unimproved or Worse	Prolonged Improvement	Remission "Cure"	Polypoid Regrowth	Reinfection	Clear
1-3	13	11	2	0	2	2	5
4-7	9	6	1	2	5	2	1
8-11	5	5	0	0	2	1	2
12-14	4	3	1	0	3	2	1
TOTALS	31	25	4	2	12	7	9

FOLLOW UP STUDY OF SINUS SURGERY IN
TABLE IX. BRONCHIAL ASTHMA

2. Without Radical Antrum Operation

Follow-up years	Cases	Asthma			Rhinologic Status		
		Unimproved or Worse	Prolonged Improvement	Remission "Cure"	Polypoid Regrowth	Reinfection	Clear
1	4	3	0	1	0	0	4
2-3	12	5	4	3	3	2	5
4-5	6	2	4	0	2	0	3
6-7	8	7	1	0	3	1	4
TOTALS	30	17	9	4	8	3	16

infection in seven. Nine cases manifested no evidence of recurrent polypoid disease or infection. Thus the final rhinologic result was unsatisfactory in the majority of our cases despite complete and repeated surgical procedures and careful postoperative care.

Of interest, too, was the often paradoxical relationship between the rhinologic status and the effect upon the asthma following radical sinus surgery. Three of the six cases with clinical improvement of the asthma, including both cases of actual "cure", showed evidence of return of polypoid disease. On the other hand, among the nine cases with good postoperative rhinologic results, only one was observed to have experienced any significant improvement of the asthma following the operative procedures.

The results in the second follow-up group without radical antrum surgery were as follows: 13 patients had a more favorable course after operation. Of these, four experienced a prolonged remission or "cure" of the asthma. Seventeen were unimproved or worse.

The postoperative rhinologic status was evaluated in 27 of the 30 cases. Polypoid regrowth was present in eight cases and gross sinus infection in three. Sixteen cases manifested no evidence of recurrent polypoid disease or infection.

Comparison of the results of the two follow-up groups shows a greater frequency of favorable effect upon the asthma in the patients who did not have radical antral surgery. While it is probable that the severity of the asthma may not have been the same in the two groups of cases, the data do illustrate that improvement of asthma and even apparent "cure" may occur *without* complete removal of presumed bacterial foci. A favorable course was observed in a minority of the cases in both groups following operation.

DISCUSSION

Our findings in this study emphasize the need for more precise criteria in the diagnosis of sinus disease as foci of infection. In vasomotor or allergic patients, the careful differentiation between infected and vasomotor secretion and membrane is of vital importance if proper therapy is to be employed.

For over 20 years the effect of sinus infection on the underlying pathologic alterations of the mucous membrane and the relationship of both to the accompanying asthma has been a matter of contro-

versy. On the one hand there has been the point of view that the sinus infection is the primary cause for the membrane changes and asthma, mediated through a mechanism of bacterial allergy.[3,4,5] The edematous, eosinophil-infiltrated sinus membrane with micro-organisms described as uniformly present deep in the tissues is offered as objective proof of bacterial allergy. Opposed to this there has been the viewpoint that sinus infection is superimposed upon an already abnormal allergic or vasomotor membrane. Those who hold this opinion have not regarded infection as the cause, either of the membrane pathology or of the accompanying asthma, although the infection may aggravate and alter the course of both.[6,7]

As evidence to support the latter concept we have submitted the following observations: *1.* Absence of infection as judged by our criteria in many instances of sinus disease; *2.* No proof of sinus infection in many cases of intrinsic asthma; *3.* The long term bacteriologic studies which suggested the occurrence of transient and multiple infections of the sinuses in asthma; *4.* The lack of consistent correlation between Roentgen and bacteriologic findings of the sinuses; *5.* The failure to demonstrate significant micro-organisms either on culture or on sections of sinus membranes which showed typical allergic pathologic alterations.

We have made a small series of observations on asthmatic responses to provocative injections of autogenous sinus vaccines. Such symptomatic asthmatic reactions have been offered as evidence of specific bacterial allergy.[8] While we do not include a report on our findings in this paper, they indicated that single positive asthma responses should be interpreted with caution. In our experience the majority of injections failed to induce asthma. These findings will be presented in detail elsewhere.

Extensive membrane disease affecting all sinuses was more common in the intrinsic than in the extrinsic asthma group, as has been previously reported by Weille.[6] This may explain the greater frequency of infection in the intrinsic cases. The proponents of the bacterial allergy theory consider these findings as supporting their concept. We consider the findings previously cited, which indicate that the sinus infection is not a causative but a superimposed factor in this disease, to be more convincing and conclusive.

At this point we should like to indicate our acceptance of the bacterial allergy hypothesis as illustrated by the initiation of a systemic disease by an upper respiratory infection. The classical example of this, of course, is the relationship of acute hemolytic streptococcal infection of the pharynx and rheumatic fever. In the course of this study, for instance, we have seen paranasal sinus infections precipitate the development of erythema nodosum and periarteritis nodosa.

In children the sequence of asthma following acute upper respiratory infections is not uncommon, although the precise mechanism remains obscure. In such instances, as in some cases of our own series with multiple pathogens, one must envision so broad a spectrum of bacterial and/or viral reactivity as to raise the question whether the reaction could be one of specific allergy.

There is a difference of opinion concerning the effectiveness of radical sinus surgery on bronchial asthma.[9,10,11,12] In our small series, improvement of asthma was twice as frequent when surgery did not include removal of antral membrane. The severity of asthma in the two patient groups may not have been comparable, and so no conclusion is offered as regards the superiority of one type of surgery over the other; however, the results are of interest in that improvement of asthma, even apparent arrest of the disease, occurred without eradication of the presumed focus of bacterial allergy.

The data gathered, we believe, also adds support to the view that the therapeutic approach to sinus disease in asthma should be conservative. The extent of treatment should be determined by the local findings rather than by the concept of bacterial allergy. The use of sinus irrigations in conjunction with antibiotic therapy, systematically and locally, is the initial treatment of choice. When postnasal discharge, even of non-infected secretion, aggravates cough or asthma, or non-infected polypoid sinus disease causes obstruction, conservative surgery may be required. Only when there is evidence of persistent infection, associated either with local symptoms or with intractable asthma, do we feel justified in contemplating the use of radical sinus surgery.

SUMMARY AND CONCLUSION.

1. Eighty-two patients with bronchial asthma had complete

sinus investigations to determine the role of sinus infection in their disease. The study included allergic, rhinologic and sinus X-ray examinations, together with microscopic and bacteriologic studies of nasal and sinus secretions. Precise criteria of infection were emphasized.

2. Among 58 cases of intrinsic asthma, 25 had sinus infection and 33 were free from infection. Among 24 extrinsic cases five had sinus infection, and 19 were free from infection. Although sinus infection was more frequent in the intrinsic group, it was present in less than half of such cases in which infection is usually considered as a causative factor.

3. Bacteriologic observations of sinus secretion made repeatedly, in some cases over many months, revealed the occurrence of transient and multiple infections. These findings suggest that the micro-organisms isolated cause infection on a previously abnormal membrane as a result of vasomotor or allergic influences rather than act as etiologic agents responsible for the altered sinus membrane.

4. In the correlation of sinus roentgenograms with bacteriologic findings, of 42 cases with positive X-rays, 24 showed sinus infection while 18 were free from infection. Of 29 cases with negative X-rays, nine showed sinus infection while 20 were free from infection. Although sinus infection was more frequently associated with abnormal sinus membrane, such membrane disease may occur without infection, and infection may occur without membrane disease in asthmatic patients.

5. Bacteriologic and micro-pathologic study of antral membrane was done in 16 cases of intrinsic asthma. In seven cases membranes showed an allergic reaction with many eosinophils, edema and thickening of basement membrane, although cultures yielded no growth or only non-pathogens. None of these showed micro-organisms on tissue sections. Four membranes with the same pathology cultured small to moderate numbers of potential pathogens. On tissue sections micro-organisms were seen localized near the surface in one membrane. Pathogens were obtained from a single allergic membrane and a few micro-organisms were seen beneath the basement membrane. Four membranes showed non-specific acute and chronic inflammation and yielded pathogens. In one of these membranes

micro-organisms were visible on section but were located superficially.

6. The findings of the membrane study indicated that hyperplastic allergic sinus membrane may occur in the absence of infection. Sinus infection when present appears to be located chiefly near the surface of the membrane.

7. A follow-up study of one to 14 years after sinus surgery in 61 asthmatic deals with two groups of cases, with and without radical antrum operation. Definite improvement in asthma occurred twice as often in the group without removal of antral membrane, although only a minority of patients were benefited in either group. Arrest of asthma may occur even though antral membrane is not removed. Significant improvement of asthma after radical sinus surgery may occur despite the regrowth of polypoid tissue, and paradoxically, there may be no improvement of asthma despite an excellent postoperative rhinologic status.

8. The findings offered in this study appear to warrant the conclusion that sinus infection, as a rule, is not a primary cause of asthma but rather a complication superimposed on altered sinus membrane.

9. The management of sinus disease should include at first conservative measures and later such surgery as dictated by local naso-sinal abnormalities and by persistent infection. The decision to employ radical sinus procedures should be determined by these factors rather than by the concept of bacterial allergy alone.

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COURSE IN RHINOPLASTY, RECONSTRUCTIVE SURGERY OF NASAL SEPTUM AND OTOPLASTY.

An intensive postgraduate course in Rhinoplasty, Reconstructive Surgery of the Nasal Septum and Otoplasty will be given July 16, 1955, to July 30, 1955, by Dr. Irving B. Goldman and staff at The Mount Sinai Hospital, New York City, in affiliation with Columbia University.

Candidates should apply to Registrar for Postgraduate Medical Instruction, The Mount Sinai Hospital, 5th Avenue and 100th Street, New York 29, New York.

OTITIC COMPLICATIONS WITH ANTIBIOTIC RESISTANT BACTERIA*†

Louis E. Silcox, M.D.
Philadelphia, Pa.

In the treatment of infections of the ear and mastoid there have been three distinct eras within the experience of our generation of otologists: the long era prior to the advent of chemotherapy and antibiotics, in which otitic infections and their complications were commonplace and temporal bone surgery for relief of these infections were daily occurrences; the second, or the antibiotic era, in which practically all infections of the ear and mastoid were controlled with the proper antibiotic, and the third in which infections of the ear and adjacent structures are not being controlled by antibiotics; and complications such as deafness, lateral sinus thrombosis, meningitis and brain abscess are being seen frequently because of the development of strains of the common pathogenic organisms which have become resistant to the various antibiotics.

The time has passed when the otologist and his referring physicians, the practitioner and pediatrician, can relax complacently behind a large dose of penicillin or other so-called miracle drugs when treating a patient with acute or chronic otitis media. In a survey of the use of antibiotics in otology one is led to the conclusion that too much reliance has been placed on them, and that many of the glowing reports of cure of mastoiditis with penicillin and other antibiotics has led physicians in general to the practices of omitting the guidance of the otologist in evaluating the ear pathology.

Complications of otitic disease are being seen and reported in ever increasing numbers, and the reasons for such reports are as follows:

1. Bacterial resistance to antibiotics due to their prolonged or indiscriminate usage. "Shotgun" therapy with antibiotics helps to develop resistant organisms.

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2. The development of mutations of bacteria which easily acquire resistance to antibiotics.
3. Widespread use of antibiotics topically as lozenges or sprays so that resistant strains or allergic reactions develop.
4. Inadequate dosage of antibiotics at the onset of an infection.
5. Use of the specific antibiotic too late in an infection after the complication has developed.
6. Use of the wrong antibiotic at the start of the infection and later shifting to the proper one.
7. Masking of continued infection or complications by antibiotics.
8. "Superinfection," a term which is applied to fresh complicating infections arising during antibiotic therapy.

Different bacterial species and strains possess varied inherent susceptibilities to drugs. In addition to the well-known resistance of the gram negative organisms to sulfonamides and penicillin, marked differences occur between drug susceptibilities of different strains of the same gram positive organism.

Since staphylococcus adapts readily to changes in environment, each drug used extensively to eliminate staphylococcal infection eventually becomes ineffective. Treatment with penicillin, streptomycin, chlortetracycline, chloramphenicol, oxytetracycline or erythromycin is often unsuccessful. Strains resistant to bacitracin or neomycin are less common.

The insensitive strains become established among persons treated with or exposed to antibacterial agents. The staphylococcus exists in the nares and on the skin and is easily disseminated by sneezing or coughing. Because of this rapid dissemination healthy persons soon become carriers of resistant strains. It has been established that 60 per cent of the strains of staphylococci are now resistant to penicillin, and the incidence is increasing rapidly. Prior to the introduction of penicillin in 1942 approximately 12 per cent of the strains of staphylococci isolated from patients were found to be naturally resistant to the drug. Over 50 per cent of the strains isolated in the latter part of 1949 and early 1950 were observed to

be highly resistant to penicillin. This demonstration of penicillin resistance *in vitro* has been correlated with the therapeutic failures, and coincides with the experience of others.

Davison suggested a few years ago that penicillin levels in 1949 had to be 15 times higher than in 1946 in order to inhibit growth of 80 per cent of gram positive cocci in nasal exudates.

Romansky pointed out before this Society a few years ago that the gram positive cocci were not only developing resistance to penicillin, but also to aureomycin, chloromycetin and terramycin.

The response of bacteria to various drugs is a complex of different factors, and the inner mechanism varies with species and with drugs so that no one explanation of drug resistance can cover more than a few individual cases.

Resistance can be developed both *in vitro* and *in vivo* by contact of the bacterium with sublethal concentrations of drug through several successive generations. Development of resistance is a gradual process, and the final degree of resistance is often dependent upon the concentration of drug employed. Resistance to high concentrations of drugs can be developed by repeated exposure to small doses.

The maximum resistance capable of being developed varies greatly with different organisms, and staphylococcus strains have been shown to develop a higher degree of resistance than streptococci or pneumococci.

The rapidity with which resistance is acquired also varies greatly with different organisms and different drugs. Once resistance has been acquired it is often, but by no means always, a fairly permanent character tic of the strain and may survive numerous transfers in the absence of the drug.

An organism rendered resistant to one drug is often found to have acquired at the same time cross resistance to chemically related drugs, and sometimes also to chemically unrelated drugs.

Micro-organisms appear to be capable of developing resistance to the majority of drugs which are employed clinically. In view of the cross resistance referred to between different groups of drugs it is obviously important that the clinician should have

information as to which groups of drugs may be usefully tried in infections with resistant strains. There is some clinical evidence that synergism occurs in certain combinations of antibiotics against resistant bacteria.

From the clinical point of view the production of the enzyme penicillinase by resistant strains is quite important, and *in vitro* tests of penicillin sensitivity should take penicillinase into consideration. Penicillinase, an enzyme that destroys penicillin, is produced by a wide variety of bacteria. There is not a direct relationship between the amount of penicillinase produced by an organism and its susceptibility to penicillin. The rapidity of production is more important than the potential of producing large amounts.

With the large number of antibiotic drugs now available, accurate and rapid diagnosis of the organism causing the infection and its sensitivity to the various antibiotics is essential to the proper treatment of the patient. With the use of discs of the antibiotics in three dilutions placed on blood agar plates with the cultured organisms accurate results can be obtained in 24 hours informing the clinician as to the causative organism and its relative resistance or degree of sensitivity to each antibiotic.

In the antibiotic era of the past 15 years the literature has been filled with miraculous cures of otogenic complications by use of chemotherapy and antimicrobial agents, and as a result there has developed among the laity and physicians alike a false sense of security, so that the otologist who suggests surgery of the ear or mastoid before the patient is moribund is viewed with suspicion. It is a well-known fact that every purulent otitis carries with it a number of potential complications, and the early recognition and treatment of these complications is all important. Many cases of fatality have been reported due to masking of the classical signs and symptoms of intracranial complication by antibiotics, and Cirillo in England states that chemotherapeutic temporizing tends to delay life-saving surgical procedures in cases of serious intracranial complications.

A case in point was reported by von Christierson. The patient was treated for otitis media for two weeks with sulfadiazine. The drum had healed, and the patient seemed well. Severe headache suddenly developed, with convulsions and vomiting, and within a

short time the patient died. An autopsy showed a healed drum, necrotic petrositis and adjacent localized meningitis and massive cerebellar abscess.

The following cases which illustrate the type of otitic complications seen with antibiotic resistant bacteria were a few of those treated on the Otolaryngologic Service at The Graduate Hospital, Philadelphia, during the past year:

Case No. 1: A 6-year-old white female was admitted in a semicomatose state with a history of an upper respiratory infection of two weeks' duration. She had developed an acute otitis media on the right side after 10 days illness. She improved clinically on penicillin therapy, but after the cessation of treatment her earache returned. A myringotomy was performed with release of purulent secretion. Again she was treated with penicillin and improved clinically; however, headache, nausea and vomiting followed, and she was admitted to a local hospital where a spinal tap revealed cloudy fluid, and the culture indicated a pneumococcus. The dosage of penicillin was increased; but no improvement was noted, and after two days the patient went into a coma and was transferred to The Graduate Hospital for further evaluation.

The physical examination at the time of admission to the hospital revealed a semi-comatose, toxic, dehydrated white female child with a positive Kernig's sign, Brudzinski sign and some opisthotonus. The temperature was 98, pulse 60 and respirations 20. Otoscopic examination revealed purulent secretions in the right canal pulsating from a small posterior attic perforation. There was an unsustained nystagmus to the right, and the fundiscopic examination was normal. She had a purulent pharyngitis and bilateral rhonchi in the upper lung fields. The spinal fluid contained 148 cells predominantly lymphocytes, and the chemistry was normal. Her blood picture showed an anemia and a leucocytosis of 16,000 with 80 percent neutrophiles. X-ray examination revealed a right acute mastoiditis with evidence of cell breakdown. The skull films were negative, and the chest plate revealed a tracheobronchitis.

It was believed that she had a subdural abscess with extension into the posterior fossa, and she was given 1,000,000 units of aqueous penicillin every two hours, 2.5 grams of sodium sulfadiazine intravenously, 500 c. c. of whole blood and fluids. Under general anesthesia a simple mastoidectomy through a post-auricular incision was performed. Immediately after the cortex was removed, a copious amount of purulent secretion exuded through the opening. The lateral sinus was already exposed by the disease and was thrombotic. This was incised and some thrombotic debri removed until there was a free flow of blood from above and below the incision.

Since this open perisinus abscess exposed the dura of the posterior fossa, and the latter was covered with granulation tissue, the cerebellum was probed for abscess, but none was located. The temporal fossa dura showed no pathology, so consequently no further attempt to uncover an abscess was made. After the lateral sinus and mastoid cavity were packed the skin incision was allowed to remain open to facilitate any future manipulation.

Culture of the material from the abscess showed beta hemolytic streptococcus and hemolytic and non-hemolytic staphylococcus aureus, which were sensitive to achromycin. 150 mg. of that antibiotic was given intravenously every six hours, along with the penicillin and sulfadiazine.

On the third post-operative day, due to a bout of respiratory depression the cerebellum was again probed through the mastoid area, but again no abscess was located. The next five days of convalescence showed no apparent improvement and on the eighth post-operative day papilledema was noted. A rotary nystagmus to the right and nucal rigidity reappeared. The pulse dropped to 68.

Because of these signs a right temporo-parietal and occipital trephine were performed; the latter releasing 20 c. c. of thin purulent material from the cerebellum. A culture of this revealed the same organisms as the perisinus abscess. After this procedure the patient improved rapidly and was discharged within two weeks. One month later the only neurologic sign present was a minimal loss of coordination in her right hand and foot.

This is a case of acute otitis, which was due to the beta hemolytic streptococcus and the hemolytic staphylococcus aureus, which were both resistant to penicillin, the antibiotic with which she was being treated when her complications developed. Despite the fact that these organisms were found to be sensitive to achromycin, I feel certain that she would not have recovered without complete surgical intervention.

Case No. 2: A 15-year-old white male was admitted with the chief complaint of earache on the left side, with discharge from that ear for one month. He had been successfully treated with antibiotics for left earache two years prior to this.

Two weeks before admission he developed headache and his earache became more severe. He had multiple injections of penicillin without improvement. Four days before admission he developed a stiff neck, and his temperature and headache increased until two days before admission, when he became nauseated, vomited several times and complained of weakness.

Physical examination revealed a semi-comatose dehydrated white male, pulse 70, respiration 24, and a temperature of 104. Otoscopic examination revealed purulent secretions in the left canal exuding from a posterior marginal perforation. The right ear was normal. Fundoscopic examination was normal, but there was noted an unsustained vertical nystagmus, and a fleeting horizontal nystagmus to the right. The mastoid tip on the left was tender to palpation.

Neurologic examination revealed a positive Kernig, Brudzinski and Babinski sign. The rest of the physical examination was essentially negative, except for some fading hemorrhagic spots in the skin of the abdomen.

A lumbar puncture revealed a pressure of 305 mm. water. The cell count of the spinal fluid was 2800 with 90 percent polymorphonuclears and 35 mg. percent of sugar. The culture was sterile. Blood culture was negative, but a culture of the secretion from the ear revealed a beta hemolytic streptococcus. It was believed he had a cerebellar abscess secondary to an acute mastoiditis.

He was given 2,000,000 units of aqueous penicillin every two hours, two grams of Benemid daily, 5 grams of sodium sulfadiazine intravenously, and 3,000 c.c. of fluid. After 24 hours of intensive antibiotic and fluid replacement therapy, a simple mastoidectomy under local an-

esthesia was performed through a post-auricular incision. The contents of the mastoid cavity consisted of necrotic bone and a small cholesteatoma in the antrum, which had penetrated the tegmen and produced granulation tissue on the dura of the middle fossa. This area was incised with a return of clear cerebrospinal fluid.

The lateral sinus was exposed, and about one ounce of pus was released from around the sinus. The posterior fossa dura was exposed, and it appeared normal except for minimal injection of the vessels and, therefore, was not incised. The lateral sinus was incised, a thrombus removed, and after a free flow of blood the sinus was packed above and below the incision.

The mastoid cavity was packed and allowed to remain open for future manipulation if necessary. The culture from the lateral sinus showed hemolytic streptococci and bacillus proteus, which were found to be resistant to all antibiotics.

The patient responded well immediately after surgery. The next morning his headache and temperature subsided, and he was more active; but 19 hours after surgery he had difficulty with his speech, developed a cough and his temperature fell rapidly to subnormal. Within the hour he turned cyanotic and a tracheotomy was performed in bed. He was given intracardiac adrenalin and central nervous system stimulants. The neurosurgical department was consulted and thought his symptoms were on a central basis due to edema and a generalized encephalitis and arachnoiditis. The otolaryngology staff felt that the posterior fossa should be incised and probed for abscess formation. This was done under aseptic technique at the bedside but revealed no purulent material.

During the next week the patient improved gradually, but still maintained a temperature between 100-102. Reculture of the mastoid showed bacillus proteus, again not sensitive to any of the antibiotics.

On the fourth post-operative day, he had a generalized convulsion. He was again re-evaluated by the Neurosurgical Department, but no procedure was advised at that time. His post-operative course for the next 10 days was relatively favorable. His temperature and pulse had returned to normal, the spinal tap was clear and showed only seven cells; the mastoid cavity was open, but no purulent secretions were present. The antibiotics had been discontinued, the packs were all out and extubation started. On the 14th post-operative day he again had a respiratory depression and succumbed 36 hours later.

At autopsy a left infratentorial abscess was found with bacillus proteus the predominate organism resistant to all antibiotics.

Case No. 3: A 68-year-old white male, with a history of left-sided earache and otorrhea of three days' duration. Two days prior to admission he had a short period of unconsciousness. Examination revealed a comatose elderly male with left-sided purulent ear discharge and mastoid tenderness. Kernig and Brudzinski's signs were positive. His temperature was 105.4 rectally and the spinal fluid showed 330 cells, and the culture was sterile. A culture of the ear discharge revealed hemolytic staphylococcus aureus and paracolon, and both organisms were resistant to all antibiotics. He was treated with large doses of sulfadiazine, penicillin and streptomycin. Two days after admission a simple mastoidectomy was done and a purulent meninigitis found. Culture from the mastoid cavity showed the same organisms as the ear discharge, and they were found to be resistant to all antibiotics. His post-operative course was stormy, but he was discharged six weeks after admission in good health.

An interesting feature of these three cases is that they all had acute and not chronic otitis media, with rapidly developing serious complications that were not controlled by antibiotics because of resistant bacteria. They all illustrate well the need for early and complete surgical intervention in otitic complications.

CONCLUSIONS

1. Bacterial resistance to antibiotics is on the increase.
2. Complications of otitic infection due to resistant organisms are being observed more frequently.
3. Sensitivity cultures in cases of otitic infection to determine the proper antibiotic is imperative.
4. Complete surgical removal of infected tissue and abscess drainage is as important as in the pre-antibiotic era.
5. It is the duty of the otologist to keep the medical profession and the public aware of the changing concepts in medical and surgical care of the ear.

BRONCHOESOPHAGOLOGY COURSE

The next Bronchoesophagology Course to be given by the University of Illinois College of Medicine is scheduled for the period October 24 to November 5, 1955, under the direction of Dr. Paul H. Holinger.

Interested registrants will please write directly to the Department of Otolaryngology, University of Illinois College of Medicine, 1853 West Polk Street, Chicago 12, Illinois.

POST-GRADUATE COURSES AT TEMPLE UNIVERSITY.

The following Post-Graduate Courses to be given in this Department during the current year:

Post-Graduate Course in Broncho-Esophagology, June 13-24, 1955; October 17 - 28, 1955.

Post-Graduate Course in Laryngology and Laryngeal Surgery, September 19 - 30, 1955.

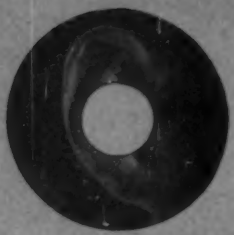
These courses are all to be given in the Department of Laryngology and Broncho-esophagology, Temple University Hospital and School of Medicine, under the direction of Dr. Chevalier L. Jackson and Dr. Charles M. Norris. The tuition fee for each course is $250.00. Further information and application blanks can be obtained from Dr. Chevalier L. Jackson, 3401 N. Broad Street, Philadelphia 40, Pennsylvania.

KENFIELD SCHOLARSHIP.

The American Hearing Society announces March 1 as opening date for competition for the 1955 Kenfield Memorial Scholarship, an award made annually to a prospective teacher of lipreading. Application blanks may be obtained by writing to the society's national headquarters, 817 14th St., N.W., Washington 5, D. C.

Deadline for returning completed applications is May 1. They are to be mailed to Mrs. Dorothy J. Cornett, 4310 S.W. 14th St., Coral Gables 34, Fla.

Winner of the Kenfield Memorial award is entitled to take a teacher training course in lipreading from any school or university in the United States acceptable to the Teachers Committee. The scholarship is to be used within one year from the date of award.



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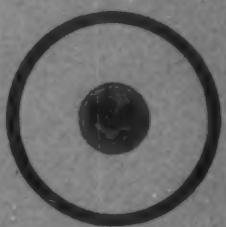

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VOLUME LXV MARCH, 1955 NUMBER 3

CONTENTS

CLINICAL APPLICATIONS OF RECRUITMENT AND MASKING. Frederick Harbert, M.D., and Joseph A. Sataloff, M.D., Philadelphia, Pa. 113

EXPERIMENTAL APPROACH TO THE STUDY OF THE COMMON COLD. Robert S. Gohd, Ph.D. (by invitation), Boston, Mass. - - 124

SECONDARY RADICAL NECK DISSECTION. John J. O'Keefe, M.D., Philadelphia, Pa. - - - - - - - - - - - - - 136

OTITIS MEDIA—THEN AND NOW. F. W. Davison, M.D., Danville, Pa. 142

SINUS DISEASE AND ASTHMA: THE PROBLEM OF FOCI OF INFECTION. Joseph L. Goldman, M.D.; Sheppard Siegal, M.D.; Leon M. Arnold, M.D.; Samuel M. Bloom, M.D.; Joseph Freeman, M.D., and Cecile Herschberger, B.S., New York, N. Y. - - - 152

OTITIC COMPLICATIONS WITH ANTIBIOTIC RESISTANT BACTERIA. Louis E. Silcox, M.D., Philadelphia, Pa. - - - - - - 170

DIRECTORY OF OTOLARYNGOLOGIC SOCIETIES - - - - - - - 179